

DESCRIPTION  
CYCLIC HEXAPEPTIDE DERIVATIVES

5 TECHNICAL FIELD

The present invention relates to new polypeptide compounds and salts thereof which are useful as a medicament.

BACKGROUND ART

- 10 In U.S. Pat. No. 5,376,634, 5,569,646, WO 96/11210 and WO 99/40108, there are disclosed the polypeptide compound and a pharmaceutically acceptable salt thereof, which have antimicrobial activities (especially antifungal activity).

15 DISCLOSURE OF INVENTION

The present invention relates to new polypeptide compound and a salt thereof.

- More particularly, it relates to new polypeptide compound and a salt thereof, which have antimicrobial activities
- 20 [especially, antifungal activities, in which the fungi may include Aspergillus, Cryptococcus, Candida, Mucor, Actinomyces, Histoplasma, Dermatophyte, Malassezia, Fusarium and the like.], inhibitory activity on  $\beta$ -1,3-glucan synthase, and further which are expected to be useful for the prophylactic and/or therapeutic
- 25 treatment of Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) in a human being or an animal, to a process for preparation thereof, to a pharmaceutical composition comprising the same, and to a method for the prophylactic and/or therapeutic treatment of infectious disease including
- 30 Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) in a human being or an animal.

- The object polypeptide compounds of the present invention are new and can be represented by the following general formula
- 35 (I):

5

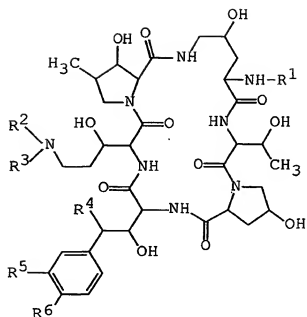
10

15

20

25

30



wherein

$R^1$  is hydrogen or acyl group,

$R^2$  is hydrogen or acyl group,

$R^3$  is lower alkyl which has one or more hydroxy or  
protected hydroxy,

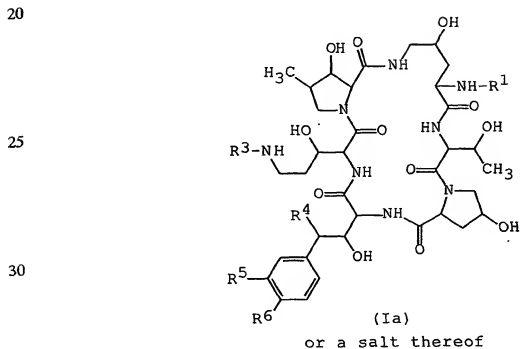
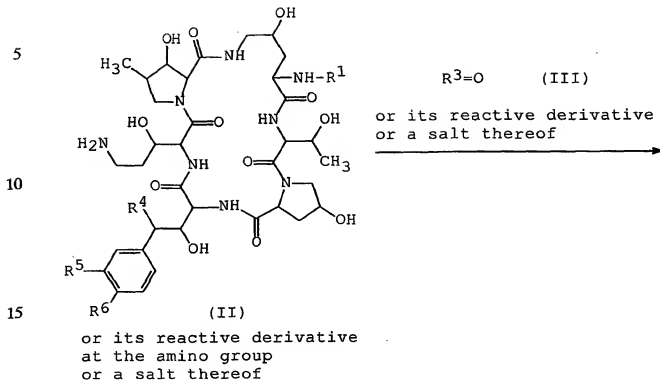
$R^4$  is hydrogen or hydroxy,

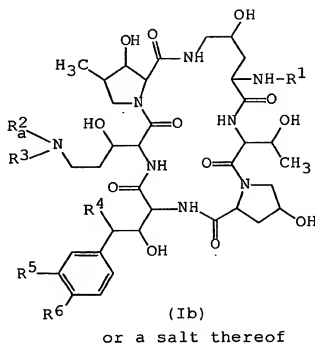
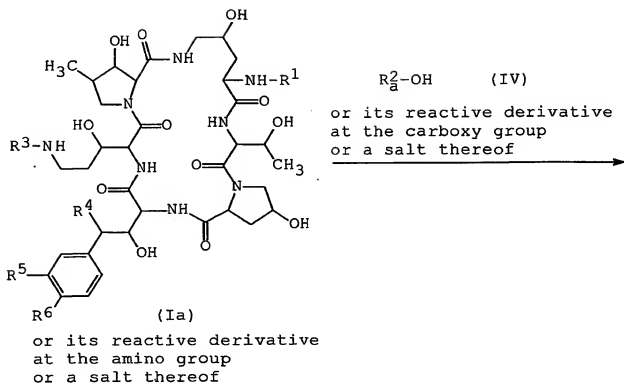
$R^5$  is hydrogen, hydroxy, lower alkoxy or hydroxysulfonyloxy, and

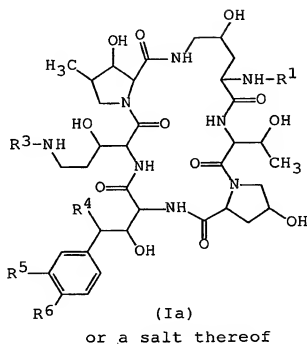
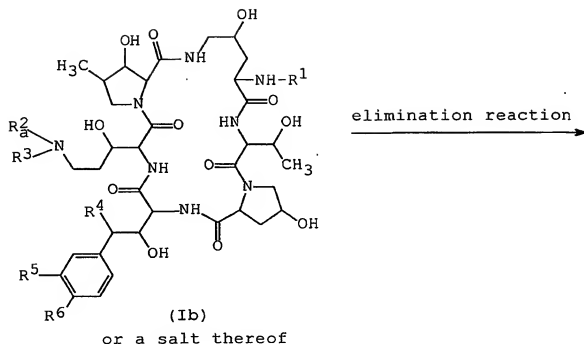
$R^6$  is hydroxy or acyloxy,

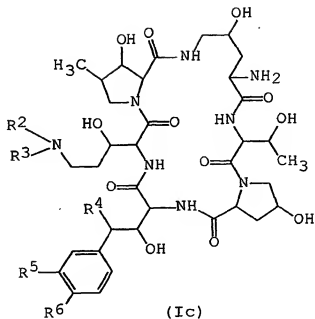
or a salt thereof.

The new polypeptide compound (I) or a salt thereof can be prepared by the process as illustrated in the following reaction schemes.

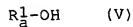
Process 1

Process 2

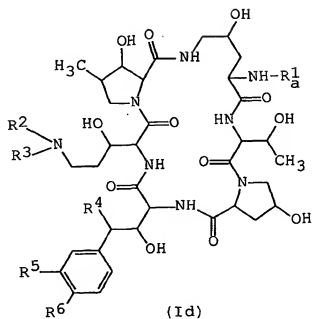
Process 3

Process 4

or its reactive derivative  
at the amino group  
or a salt thereof



or its reactive derivative  
at the carboxy group  
or a salt thereof



or a salt thereof

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and  $R^6$  are defined above,

$R_a^1$  is acyl group, and

$R_a^2$  is acyl group.

- 5        Suitable salt of the new polypeptide compound (I) is a pharmaceutically acceptable and conventional non-toxic salt, and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth
- 10    metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt;
- a salt with an organic base, for example, an organic amine salt (e.g., triethylamine salt, diisopropylethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt,
- 15    dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, 4-dimethylaminopyridine salt, etc.);
- an inorganic acid addition salt (e.g., hydrochloride hydrobromide, sulfate, phosphate, etc.);
- 20    an organic carboxylic sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.);
- a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

- 25        Suitable examples and illustration of the various definitions in the above and subsequent descriptions of the present specification, which the present invention intends to include within the scope thereof, are explained in detail as
- 30    follows:

      The term "lower" is used to intend a group having 1 to 6 carbon atom(s), unless otherwise provided.

- 35        Suitable example of "one or more" may be the number of 1 to 6, in which the preferred one may be the number of 1 to 3, and

the most preferred one may be the number of 1 or 2.

Suitable example of "halogen" may be fluorine, chlorine, bromine, iodine and the like.

Suitable example of "lower alkoxy" may include straight or  
5 branched one such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, tert-pentyloxy, neo-pentyloxy, hexyloxy, isohexyloxy and the like.

Suitable example of "higher alkoxy" may include straight or  
branched one such as heptyloxy, octyloxy,  
10 3,5-dimethyloctyloxy, 3,7-dimethyloctyloxy, nonyloxy, decyloxy, undecyloxy, dodecyloxy, tridecyloxy, tetradecyloxy, hexadecyloxy, heptadecyloxy, octadecyloxy, nonadecyloxy, icosyloxy, and the like.

Suitable example of "lower alkyl" may include straight or  
15 branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl, neo-pentyl, hexyl, isohexyl and the like.

Suitable example of "higher alkyl" may include straight or  
branched one such as heptyl, octyl, 3,5-dimethyloctyl, 3,7-  
20 dimethyloctyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, and the like.

Suitable example of "aryl" and "ar" moiety may include  
phenyl which may have lower alkyl (e.g., phenyl, mesityl, xylyl,  
25 tolyl, etc.), naphthyl, anthryl, indanyl, fluorenyl, and the like, and this "aryl" and "ar" moiety may have one or more halogen.

Suitable example of "aroyl" may include benzoyl, toluoyl, naphthoyl, anthrylcarbonyl, and the like.

Suitable example of "heterocyclic group" may include  
30 unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g.



1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, azetidyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indoliziny, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

10 unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

15 saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, morpholino, etc.;

20 unsaturated condensed heterocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

25 unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;

30 saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example thiazolidinyl, thiomorpholinyl, thiomorpholino, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s), for example, thienyl, dihydrodithiynyl, dihydrodithionyl, etc.;

35 unsaturated condensed heterocyclic group containing 1 or 2

sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, imidazothiadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s), for example, tetrahydrofuran, tetrahydropyran, dioxacyclopentane, dioxacyclohexane, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 or 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s), for example benzothienyl, benzodithiinyl, etc.;

unsaturated condensed heterocyclic group containing an oxygen atom and 1 or 2 sulfur atom(s), for example, benzoxathiinyl, etc.; and the like, and this "heterocyclic group" may have one or more suitable substituent(s) selected from the group consisting of lower alkyl, oxo, cyclo(lower)alkyl, hydroxy(lower)alkyl, carboxy(lower)alkanoyl which may have amino and heterocycliccarbonyl.

Suitable example of "cyclo(lower)alkyl" may include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like, and this "cyclo(lower)alkyl" may have one or more lower alkyl.

Suitable example of "cyclo(lower)alkyloxy" may include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

Suitable example of "acyl group" may include aliphatic acyl, aromatic acyl, arylaliphatic acyl and heterocyclic-aliphatic acyl derived from carboxylic acid, carbonic acid, carbamic acid, sulfonic acid, and the like.

Suitable example of said "acyl group" may be illustrated as follows.

Carboxy; carbamoyl; mono or di(lower)alkylcarbamoyl (e.g., methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, etc.)

- 5 Aliphatic acyl such as lower or higher alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.);
- 10 lower or higher alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, heptyloxycarbonyl, etc.); lower alkenyloxycarbonyl (e.g., vinyloxycarbonyl, propenyloxycarbonyl, allyloxycarbonyl, butenyloxycarbonyl, butadienyloxycarbonyl, pentenyloxycarbonyl, hexenyloxycarbonyl, etc.);
- 15 lower or higher alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.);
- lower or higher alkoxysulfonyl (e.g., methoxysulfonyl, ethoxysulfonyl, etc.); or the like;
- 20 Aromatic acyl such as
- aroyl (e.g., benzoyl, toluoyl, naphthoyl, etc.);
- ar(lower)alkanoyl [e.g., phenyl(C<sub>1</sub>-C<sub>6</sub>)alkanoyl (e.g., phenylacetyl, phenylpropanoyl, phenylbutanoyl,
- 25 phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(C<sub>1</sub>-C<sub>6</sub>)alkanoyl (e.g., naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, etc.), etc.];
- ar(lower)alkenoyl [e.g., phenyl(C<sub>3</sub>-C<sub>6</sub>)alkenoyl (e.g., phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl,
- 30 phenylpentanoyl, phenylhexenoyl, etc.), naphthyl(C<sub>3</sub>-C<sub>6</sub>)alkenoyl (e.g., naphthylpropenoyl, naphthylbutenoyl, etc.), etc.];
- ar(lower)alkoxycarbonyl [e.g., phenyl(C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl (e.g., benzyloxycarbonyl, etc.), fluorenyl(C<sub>1</sub>-C<sub>6</sub>)alkoxy-
- 35 carbonyl (e.g., fluorenylmethyloxycarbonyl, etc.), etc.];

aryloxycarbonyl (e.g., phenoxycarbonyl, naphthylloxycarbonyl, etc.);

aryloxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl, etc.);

- 5 arylcarbamoyl (e.g., phenylcarbamoyl, etc.);  
arylthiocarbamoyl (e.g., phenylthiocarbamoyl, etc.);  
arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthylglyoxyloyl, etc.);

- arylsulfonyl which may have 1 to 4 lower alkyl (e.g.,  
10 phenylsulfonyl, p-tolylsulfonyl, etc.);  
aroyl (e.g., benzoyl) substituted with one or more suitable substituent(s); or the like;

Heterocyclic acyl such as

heterocycliccarbonyl;

- 15 heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl, heterocyclicpropanoyl, heterocyclicbutanoyl, heterocyclicpentanoyl, heterocyclichexanoyl, etc.);  
heterocyclic(lower)alkenoyl (e.g., heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl,  
20 heterocyclichexenoyl, etc.);  
heterocyclicglyoxyloyl; or the like;  
in which suitable "heterocyclic" moiety in the terms  
"heterocycliccarbonyl", "heterocyclic(lower)alkanoyl",  
"heterocyclic(lower)alkenoyl" and "heterocyclicglyoxyloyl" can  
25 be referred to aforementioned "heterocyclic" moiety.

- Suitable example of "acyl group" of  $R^1$  can be referred to  
aforementioned "acyl group", in which the preferred one may be  
lower alkoxycarbonyl, higher alkanoyl and benzoyl substituted  
30 with one or more suitable substituent(s).

- Suitable example of "suitable substituent(s)" in the term  
of "benzoyl substituted with one or more suitable substituent(s)"  
may be thiadiazolyl substituted with phenyl having phenyl  
35 substituted with morpholino having lower alkyl,

- thiadiazolyl substituted with phenyl having a suitable substituent selected from the group consisting of lower alkoxy(lower)alkoxy and lower alkoxy(higher)alkoxy,
- 5 piperazinyl substituted with phenyl having piperidyl substituted with a suitable substituent selected from the group consisting of phenyl having lower alkoxy(lower)alkoxy, cyclo(lower)alkyloxy and lower alkoxy(lower)alkylthio,
- piperazinyl substituted with phenyl having phenyl substituted with morpholino having lower alkyl,
- 10 imidazothiadiazolyl substituted with phenyl having piperidyl substituted with a suitable substituent selected from the group consisting of lower alkoxy(lower)alkoxy and lower alkoxy(lower)alkylthio,
- imidazothiadiazolyl substituted with phenyl having lower
- 15 alkoxy(lower)alkoxy,
- phenyl substituted with piperazinyl having phenyl substituted with morpholino having lower alkyl,
- isoxazolyl substituted with phenyl having lower alkoxy(lower)alkoxy,
- 20 isoxazolyl substituted with phenyl having higher alkoxy substituted with morpholino having lower alkyl,
- thiadiazolyl substituted with phenyl having piperazinyl substituted with cyclo(lower)alkyl which has one or more suitable substituent(s) selected from the group consisting of lower alkyl,
- 25 lower alkenyl, lower alkoxy(higher)alkoxy and phenyl,
- thiadiazolyl substituted with phenyl having piperazinyl substituted with lower alkyl having cyclo(lower)alkyl,
- thiadiazolyl substituted with phenyl having piperidyl substituted with one or more suitable substituent(s) selected
- 30 from the group consisting of cyclo(lower)alkyloxy, lower alkoxy(lower)alkoxy and lower alkoxy(lower)alkoxy(lower)alkyl,
- thiadiazolyl substituted with phenyl having piperidyl substituted with cyclo(lower)alkyl and lower alkoxy,
- thiadiazolyl substituted with pyridyl having piperazinyl
- 35 substituted with cyclo(lower)alkyl having lower alkyl,

imidazothiadiazolyl substituted with phenyl having  
piperidyl substituted with cyclo(lower) alkyl,

imidazothiadiazolyl substituted with phenyl having  
piperazinyl substituted with cyclo(lower)alkyl having lower  
5 alkyl,

phenyl substituted with piperazinyl having  
cyclo(lower)alkyl substituted with one or more suitable  
substituent(s) selected from the group consisting of  
cyclo(lower)alkyl which may have lower alkoxy, lower alkyl, lower  
10 alkoxy and phenyl which may have lower alkoxy,

in which the preferred one may be thiadiazolyl substituted  
with phenyl having phenyl substituted with morpholino having  
dimethyl,

15 thiadiazolyl substituted with phenyl having a substituent  
selected from the group consisting of methoxyhexyloxy and  
methoxyheptyloxy,

piperazinyl substituted with phenyl having piperidyl  
substituted with a substituent selected from the group consisting  
20 of phenyl having methoxybutoxy, cyclohexyloxy and  
methoxyhexylthio,

piperazinyl substituted with phenyl having phenyl  
substituted with morpholino having dimethyl,

imidazothiadiazolyl substituted with phenyl having  
25 piperidyl substituted with a substituent selected from the group  
consisting of methoxypropoxy, methoxybutoxy, methoxypentyloxy  
and methoxyhexylthio,

imidazothiadiazolyl substituted with phenyl having  
methoxybutoxy,

30 phenyl substituted with piperazinyl having phenyl  
substituted with morpholino having dimethyl,

isoxazolyl substituted with phenyl having  
methoxyhexyloxy,

isoxazolyl substituted with phenyl having heptyloxy  
35 substituted with morpholino having dimethyl,

thiadiazolyl substituted with phenyl having piperazinyl substituted with cyclohexyl which has one or two substituent(s) selected from the group consisting of methyl, methylene, methoxyheptyloxy, methoxyoctyloxy and phenyl,

5       thiadiazolyl substituted with phenyl having piperazinyl substituted with methyl which has a substituent selected from the group consisting of cyclopentyl and cyclohexyl,

          thiadiazolyl substituted with phenyl having piperidyl substituted with one or two substituent(s) selected from the  
10   group consisting of cyclohexyl, methoxy, cyclohexyloxy, methoxypentyloxy, methoxyhexyloxy, methoxybutoxymethyl and methoxypentyloxymethyl,

          thiadiazolyl substituted with pyridyl having piperazinyl substituted with cyclohexyl which has a substituent selected from  
15   the group consisting of methyl and ethyl,

          imidazothiadiazolyl substituted with phenyl having piperidyl substituted with cyclohexyl,

          imidazothiadiazolyl substituted with phenyl having piperazinyl substituted with cyclohexyl having methyl,

20   phenyl substituted with piperazinyl having cyclohexyl substituted with one or two substituent(s) selected from the group consisting of ethyl, t-butyl, methoxy, cyclopentyl, cyclohexyl which may have methoxy or dimethyl, and phenyl which may have methoxy.

25

          The more suitable example of "acyl group" may be benzoyl which has thiadiazolyl substituted with phenyl having phenyl substituted with morpholino having dimethyl, benzoyl which has thiadiazolyl substituted with phenyl  
30   having a substituent selected from the group consisting of methoxyhexyloxy and methoxyheptyloxy, -

          benzoyl which has piperazinyl substituted with phenyl having piperidyl substituted with a substituent selected from the group consisting of phenyl having methoxybutoxy, cyclohexyloxy  
35   and methoxyhexylthio,

benzoyl which has piperazinyl substituted with phenyl having phenyl substituted with morpholino having dimethyl,

- benzoyl which has imidazothiadiazolyl substituted with phenyl having piperidyl substituted with a substituent selected  
5 from the group consisting of methoxypropoxy, methoxybutoxy, methoxypropyloxy and methoxyhexylthio,

benzoyl which has imidazothiadiazolyl substituted with phenyl having methoxybutoxy,

- benzoyl which has phenyl substituted with piperazinyl  
10 having phenyl substituted with morpholino having dimethyl,

benzoyl which has isoxazolyl substituted with phenyl having methoxyhexyloxy,

benzoyl which has isoxazolyl substituted with phenyl having heptyloxy substituted with morpholino having dimethyl,

- benzoyl which has thiadiazolyl substituted with phenyl  
15 having piperazinyl substituted with cyclohexyl which has one or two substituent(s) selected from the group consisting of methyl, methylene, methoxyheptyloxy, methoxyoctyloxy and phenyl,

- benzoyl which has thiadiazolyl substituted with phenyl  
20 having piperazinyl substituted with methyl which has a substituent selected from the group consisting of cyclopentyl and cyclohexyl,

- benzoyl which has thiadiazolyl substituted with phenyl having piperidyl substituted with one or two substituent(s)  
25 selected from the group consisting of cyclohexyl, methoxy, cyclohexyloxy, methoxypropyloxy, methoxyhexyloxy, methoxybutoxymethyl and methoxypropyloxymethyl,

- benzoyl which has thiadiazolyl substituted with pyridyl having piperazinyl substituted with cyclohexyl which has a  
30 substituent selected from the group consisting of methyl and ethyl,

benzoyl which has imidazothiadiazolyl substituted with phenyl having piperidyl substituted with cyclohexyl,

- benzoyl which has imidazothiadiazolyl substituted with  
35 phenyl having piperazinyl substituted with cyclohexyl having



methyl,

benzoyl which has phenyl substituted with piperazinyl having cyclohexyl substituted with one or two substituent(s) selected from the group consisting of ethyl, t-butyl, methoxy, 5 cyclopentyl, cyclohexyl which may have methoxy or dimethyl, and phenyl which may have methoxy.

Suitable example of "lower alkyl" in the term of "lower alkyl" which has one or more hydroxy or protected hydroxy" can be 10 referred to aforementioned "lower alkyl", in which the preferred one may be methyl, ethyl, propyl, isopropyl, butyl, pentyl and hexyl.

Suitable example of "hydroxy protective group" in the term of "protected hydroxy" may include acyl (e.g., lower 15 alkanoyl, etc.) as mentioned above, phenyl(lower)alkyl which may have one or more suitable substituent(s) (e.g., benzyl, 4-methoxybenzyl, trityl, etc.), tri-substituted silyl [e.g., tri(lower)alkylsilyl (e.g., trimethylsilyl, t-butyl 20 dimethylsilyl, etc.), etc.], tetrahydropyranyl and the like.

Suitable example of "lower alkyl which has one or more hydroxy or protected hydroxy" may be dihydroxypropyl, dihydroxyisopropyl, trihydroxybutyl, tetrahydroxypentyl, 25 pentahydroxyhexyl and diacetyloxyisopropyl.

Suitable example of "acyl group" of  $R^2$  can be referred to aforementioned "acyl group", in which the preferred one may be "amino protective group" mentioned below, and the most preferred one may be acetyl, 2-acetyloxypropionyl, methylsulfonyl, 2,5- 30 daminopentanoyl, benzyloxycarbonyl, fluorenylmethoxycarbonyl, allyloxycarbonyl and tert-butoxycarbonyl.

Suitable example of "amino protective group" may be included in aforementioned "acyl group", a conventional protective group 35 such as ar(lower)alkoxycarbonyl and lower alkoxycarbonyl, in

which the preferred one may be phenyl-  
(C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl and fluorenyl(C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl and (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, and the most preferred one may be  
benzyloxycarbonyl, fluorenylmethoxycarbonyl and tert-  
5 butoxycarbonyl.

Suitable example of "acyl" moiety of "acyloxy" can be  
referred to aforementioned "acyl group", in which the preferred  
one may be lower alkenyloxycarbonyl, and the most preferred one  
10 may be allyloxycarbonyl.

Suitable example of "acyloxy" may be lower  
alkenyloxycarbonyloxy, and the more preferred one may be  
allyloxycarbonyloxy.

15 Particularly, the preferred examples of the cyclic  
polypeptide compound (I) of the present invention are as follows:

the compound (I), wherein

R<sup>1</sup> is hydrogen, lower alkoxycarbonyl, higher alkanoyl or  
20 benzoyl substituted with one or more suitable  
substituent(s),  
R<sup>2</sup> is hydrogen,  
R<sup>3</sup> is lower alkyl which has one or more hydroxy,  
R<sup>4</sup> is hydrogen or hydroxy;  
25 R<sup>5</sup> is hydroxy or hydroxysulfonyloxy; and  
R<sup>6</sup> is hydroxy.

And, more preferred one may be the compound (I)  
wherein

30 R<sup>1</sup> is hydrogen, lower alkoxycarbonyl, higher alkanoyl or  
benzoyl substituted with one or more suitable  
substituent(s),  
R<sup>2</sup> is hydrogen,  
R<sup>3</sup> is lower alkyl which has two hydroxy,  
35 R<sup>4</sup> is hydrogen or hydroxy;

R<sup>5</sup> is hydroxy or hydroxysulfonyloxy; and  
R<sup>6</sup> is hydroxy.

And, still more preferred one may be the compound (I)

5 wherein

R<sup>1</sup> is benzoyl substituted with a suitable substituent  
selected from the group consisting of

thiadiazolyl substituted with phenyl having phenyl  
substituted with morpholino having lower alkyl,

10 thiadiazolyl substituted with phenyl having a suitable  
substituent selected from the group consisting of lower  
alkoxy(lower)alkoxy and lower alkoxy(higher)alkoxy,

piperazinyl substituted with phenyl having piperidyl  
substituted with a suitable substituent selected from the group  
15 consisting of phenyl having lower alkoxy(lower)alkoxy,  
cyclo(lower)alkyloxy and lower alkoxy(lower)alkylthio,

piperazinyl substituted with phenyl having phenyl  
substituted with morpholino having lower alkyl,

20 imidazothiadiazolyl substituted with phenyl having  
piperidyl substituted with a suitable substituent selected from  
the group consisting of lower alkoxy(lower)alkoxy and lower  
alkoxy(lower)alkylthio,

imidazothiadiazolyl substituted with phenyl having lower  
alkoxy(lower)alkoxy,

25 phenyl substituted with piperazinyl having phenyl  
substituted with morpholino having lower alkyl,

isoxazolyl substituted with phenyl having lower  
alkoxy(lower)alkoxy,

30 isoxazolyl substituted with phenyl having higher alkoxy  
substituted with morpholino having lower alkyl,

thiadiazolyl substituted with phenyl having piperazinyl  
substituted with cyclo(lower)alkyl which has one or more suitable  
substituent(s) selected from the group consisting of lower alkyl,  
lower alkenyl, lower alkoxy(higher)alkoxy and phenyl,

35 thiadiazolyl substituted with phenyl having piperazinyl

- substituted with lower alkyl having cyclo(lower)alkyl,  
thiadiazolyl substituted with phenyl having piperidyl  
substituted with one or more suitable substituent(s) selected  
from the group consisting of cyclo(lower)alkyloxy, lower  
5 alkoxy(lower)alkoxy and lower alkoxy(lower)alkoxy(lower)alkyl,  
thiadiazolyl substituted with phenyl having piperidyl  
substituted with cyclo(lower)alkyl and lower alkoxy,  
thiadiazolyl substituted with pyridyl having piperazinyl  
substituted with cyclo(lower)alkyl having lower alkyl,  
10 imidazothiadiazolyl substituted with phenyl having  
piperidyl substituted with cyclo(lower) alkyl,  
imidazothiadiazolyl substituted with phenyl having  
piperazinyl substituted with cyclo(lower)alkyl having lower  
alkyl, and  
15 phenyl substituted with piperazinyl having  
cyclo(lower)alkyl substituted with one or more suitable  
substituent(s) selected from the group consisting of  
cyclo(lower)alkyl which may have lower alkoxy, lower alkyl, lower  
alkoxy and phenyl which may have lower alkoxy,  
20  $R^2$  is hydrogen,  
 $R^3$  is lower alkyl which has two hydroxy,  
 $R^4$  is hydrogen or hydroxy;  
 $R^5$  is hydroxy or hydroxysulfonyloxy; and  
 $R^6$  is hydroxy.

25

And, the most preferred one may be the compound (I)  
wherein

- $R^1$  is benzoyl which has thiadiazolyl substituted with phenyl  
having piperazinyl substituted with cyclo(lower)alkyl which has  
30 lower alkyl,

benzoyl which has thiadiazolyl substituted with  
phenyl having piperidyl substituted with  
cyclo(lower)alkyloxy,

- benzoyl which has phenyl substituted with piperazinyl  
35 having cyclo(lower)alkyl substituted with

cyclo(lower)alkyl and lower alkoxy,  
benzoyl which has thiadiazolyl substituted with  
phenyl having piperidyl substituted with  
cyclo(lower)alkyl,

- 5           R<sup>2</sup> is hydrogen,  
          R<sup>3</sup> is lower alkyl which has two hydroxy,  
          R<sup>4</sup> is hydrogen or hydroxy;  
          R<sup>5</sup> is hydroxy or hydroxysulfonyloxy; and  
          R<sup>6</sup> is hydroxy.

10

The processes for preparing the polypeptide compound (I) of  
the present invention are explained in detail in the following.

15   Process 1

The object compound (Ia) or a salt thereof can be prepared  
by reacting the compound (II) or its reactive derivative at the  
amino group or a salt thereof with the compound (III) of the  
formula:

20



or its reactive derivative, or a salt thereof.

- 25           Suitable reactive derivative of the compound (III) may  
include an acid halide, an acid anhydride, an activated ester,  
and the like. The suitable example may be an acid chloride; acid  
azide; a mixed acid anhydride with an acid such as substituted  
phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric  
30   acid, diphenylphosphoric acid, dibenzylphosphoric acid,  
halogenated phosphoric acid, etc.), dialkylphosphorous acid,  
sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g.,  
methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid,  
alkylcarbonic acid, aliphatic carboxylic acid (e.g., pivalic  
35   acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid,

- trichloroacetic acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester (e.g., cyanomethyl, ester methoxymethyl ester, dimethyliminomethyl [(CH<sub>3</sub>)<sub>2</sub>N<sup>+</sup>=CH-] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthioester,
- 10 p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.); an ester with a N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide,
- 15 N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.); and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (III) to be used.

- The reaction is usually carried out in a conventional
- 20 solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which do not adversely affect the reaction, or the mixture thereof.

- 25 When the compound (III) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diisopropylcarboximide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N-carboxyl-bis(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine, ethoxyacetylene; 1-alkoxy-1-chloroethylene;
- 35 trialkyl phosphite; isopropyl polyphosphate; phosphorous

oxychloride (phosphoryl chloride); phosphorous trichloride;  
 thionyl chloride; oxalyl chloride; triphenylphosphite;  
 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-  
 sulfophenyl)isoxazolium hydroxide intra-molecular salt;  
 5 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole;  
 so-called Vilsmeier reagent prepared by the reaction of  
 N,N-dimethylformamide with thionyl chloride, phosgene,  
 phosphorous oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an  
 10 organic or inorganic base such as an alkali metal bicarbonate,  
 tri(lower)alkylamine (e.g., triethylamine,  
 diisopropylethylamine, etc.), pyridine,  
 di(lower)alkylaminopyridine (e.g., 4-dimethylaminopyridine,  
 etc.) N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine,  
 15 or the like.

The reaction temperature is not critical, and the reaction  
 is usually carried out under cooling to heating.

## Process 2

20 The object compound (Ib) or a salt thereof can be prepared  
 by reacting the compound (Ia) or its reactive derivative at the  
 amino group or a salt thereof with the compound (IV) of the  
 formula:



(wherein  $R_a^2$  is acyl group)  
 or its reactive derivative at the carboxy group or a salt thereof.

30 Suitable reactive derivative of the compound (IV) may  
 include an acid halide, an acid anhydride, an activated ester,  
 and the like. The suitable example may be an acid chloride; acid  
 azide; a mixed acid anhydride with an acid such as substituted  
 phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric  
 35 acid, diphenylphosphoric acid, dibenzylphosphoric acid,

halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g., methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g., pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester (e.g., cyanomethyl, ester methoxymethyl ester, dimethyliminomethyl  $[(CH_3)_2\overset{+}{N}=CH-]$  ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.); an ester with a N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.); and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (IV) to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which do not adversely affect the reaction, or the mixture thereof.

When the compound (IV) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diisopropylcarboxi-



- imide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide;  
N,N-carbonyl-bis(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine, ethoxyacetylene; 1-alkoxy-1-chloroethylene;
- 5 trialkyl phosphite; isopropyl polyphosphate; phosphorous oxychloride (phosphoryl chloride); phosphorous trichloride; thionyl chloride; oxalyl chloride; triphenylphosphite; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulphophenyl)isoxazolium hydroxide intra-molecular salt;
- 10 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, phosphorous oxychloride, etc.; or the like.

- The reaction may also be carried out in the presence of an
- 15 organic or inorganic base such as an alkali metal bicarbonate, tri(lower)alkylamine (e.g., triethylamine, diisopropylethylamine, etc.), pyridine, di(lower)alkylaminopyridine (e.g., 4-dimethylaminopyridine, etc.) N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine,
- 20 or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

### Process 3

- 25 The object compound (Ia) or a salt thereof can be prepared by subjecting a compound (Ib) or a salt thereof to elimination reaction of the acyl group.

This reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the like.

- 30 The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid. Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof,
- 35 trialkylamine [e.g. trimethylamine, triethylamine, etc.],

picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, 5 acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.]. The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, 10 trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as 15 water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under 20 cooling to warming.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or 25 metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are 30 conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, 35 colloidal palladium, palladium on barium, sulfate, palladium on

barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc], iron catalysts [e.g. reduced iron, Raney iron, etc], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

#### Process 4

The object compound (Id) or a salt thereof can be prepared by reacting the compound (Ic) or its reactive derivative at the amino group or a salt thereof with the compound (V) of the formula:



(wherein  $R_a^1$  is acyl group)  
or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the carboxy group of the compound (V) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.],

- dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g., methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g., acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid trichloroacetic acid, etc.]; or aromatic carboxylic acid [e.g., benzoic acid, etc.]; a symmetrical acid, anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole, tetrazole or 1-hydroxy-1H-benzotriazole; or an activated ester [e.g., cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [(CH<sub>3</sub>)<sub>2</sub>N<sup>+</sup>=CH-] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachloropentyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (V) to be used.

- Suitable salts of the compound (V) and its reactive derivative can be referred to the ones as exemplified for the polypeptide compound (I).

- The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

- In this reaction, when the compound (V) is used in a free acid form or its salt form, the reaction is preferably carried

- out in the presence of a conventional condensing agent such as  
N,N'-dicyclohexylcarbodiimide;  
N-cyclohexyl-N'-morpholinoethylcarbodiimide;  
N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide;  
5 N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide;  
N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide;  
N,N-carbonylbis-(2-methylimidazole);  
pentamethyleneketene-N-cyclohexylimine;  
diphenylketene-N-cyclohexylimine, ethoxyacetylene;  
10 1-alkoxy-2-chloroethylene; trialkyl phosphite;  
ethyl polyphosphate; isopropyl polyphosphate; phosphorus  
oxychloride (phosphoryl chloride);  
phosphorus trichloride; thionyl chloride; oxalyl chloride;  
lower alkyl haloformate [e.g., ethyl chloroformate, isopropyl  
15 chloroformate, etc.]; triphenylphosphine;  
2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-  
(m-sulfophenyl)isoxazolium hydroxide intramolecular salt;  
1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole;  
so-called Vilsmeier reagent prepared by the reaction of  
20 N,N-dimethylformamide with thionyl chloride, phosgene,  
trichloromethyl chloroformate, phosphorous oxychloride,  
methanesulfonyl chloride, etc.; or the like.

- The reaction may also be carried out in the presence of an  
inorganic or organic base such as an alkali metal carbonate,  
25 alkali metal bicarbonate, tri(lower)alkylamine (e.g.,  
triethylamine, diisopropylethylamine, etc.),  
pyridine, di(lower)alkylaminopyridine (e.g.,  
4-dimethylaminopyridine, etc.), N-(lower)alkylmorpholine,  
N,N-di(lower)alkylbenzylamine, or the like.

- 30 The reaction temperature is not critical, and the reaction  
is usually carried out under cooling to warming.

- The compounds obtained by the above Processes 1 to 4 can be  
isolated and purified by a conventional method such as  
35 pulverization, recrystallization, column-chromatography,

high-performance liquid chromatography (HPLC), reprecipitation, desalting resin column chromatography, or the like.

The compounds obtained by the above Processes 1 to 4 may be obtained as its solvate (e.g., hydrate, ethanolate, etc.), and  
5 its solvate (e.g., hydrate, ethanolate, etc.) is included within the scope of the present invention.

It is to be noted that each of the polypeptide compound (I) may include one or more stereoisomer such as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) and  
10 double bond(s) and all such isomers and the mixture thereof are included within the scope of the present invention.

The polypeptide compound (I) or a salt thereof may include solvated compound [e.g., hydrate, ethanolate, etc.].

The polypeptide compound (I) or a salt thereof may include  
15 both its crystal form and non-crystal form.

It should be understood that the polypeptide compound (I) of the present invention may include the prodrug form.

The patent applications and publications cited herein are incorporated by reference.  
20

In order to show the usefulness of the polypeptide compound (I) of the present invention, the biological data of the representative compound is explained in the following.

25                    Biological property of the polypeptide  
                     compound (I) of the present invention

Test (Antimicrobial activity):

' In vitro antimicrobial activity of the object compound of  
30 Examples 4, 9, 25 and 30 disclosed later was determined by MIC<sub>s</sub> in mouse serum as described below.

Test Method:

The MIC<sub>s</sub> in mouse serum were determined by the microdilution  
35 method using ICR mouse serum buffered with 20 mM HEPES buffer (pH

7.3) as a test medium. Inoculum suspension of  $10^6$  cells/ml were prepared by a hemocytometric procedure and diluted to obtain an inoculum size of approximately  $1.0 \times 10^3$  cells/ml. Microplates were incubated at 37°C for 24 hours in 5% CO<sub>2</sub>. The MIC<sub>s</sub> were defined as the lowest concentrations at which no visible growth was observed.

Test Result:

10

MIC (μg/ml)	
Test organism	Candida albicans FP-633
Test compound	
The object compound of <u>Example 4</u>	< 0.3
The object compound of <u>Example 9</u>	< 0.3
The object compound of <u>Example 25</u>	< 0.3
The object compound of <u>Example 30</u>	< 0.3

From the test result, it is realized that the polypeptide compound (I) of the present invention has an antimicrobial activity (especially, antifungal activity).

15

In more details, the polypeptide compound (I) of the present invention have an antifungal activity, particularly against the following fungi.

20

*Acremonium*;

*Absidia* (e.g., *Absidia corymbifera*, etc);

*Aspergillus* (e.g., *Aspergillus clavatus*, *Aspergillus flavus*,

*Aspergillus fumigatus*, *Aspergillus nidulans*, *Aspergillus niger*,

*Aspergillus terreus*, *Aspergillus versicolor*, etc); *Blastomyces*

- (e.g., *Blastomyces dermatitidis*, etc);  
*Candida* (e.g., *Candida albicans*, *Candida glabrata*, *Candida guilliermondii*, *Candida kefyr*, *Candida krusei*, *Candida parapsilosis*, *Candida stellatoidea*, *Candida tropicalis*, *Candida utilis*, etc.);
- 5 *Cladosporium* (e.g., *Cladosporium trichloides*, etc);  
*Coccidioides* (e.g., *Coccidioides immitis*, etc);  
*Cryptococcus* (e.g., *Cryptococcus neoformans*, etc);  
*Cunninghamella* (e.g., *Cunninghamella elegans*, etc);
- 10 *Dermatophyte*;  
*Exophiala* (e.g., *Exophiala dermatitidis*, *Exophiala spinifera*, etc);  
*Epidermophyton* (e.g., *Epidermophyton floccosum*, etc);  
*Fonsecaea* (e.g., *Fonsecaea pedrosoi*, etc);
- 15 *Fusarium* (e.g., *Fusarium solani*, etc);  
*Geotrichum* (e.g., *Geotrichum candidum*, etc);  
*Histoplasma* (e.g., *Histoplasma capsulatum* var. *capsulatum*, etc).  
*Malassezia* (e.g., *Malassezia furfur*, etc);  
*Microsporum* (e.g., *Microsporum canis*, *Microsporum gypseum*, etc);
- 20 *Mucor*;  
*Paracoccidioides* (e.g., *Paracoccidioides brasiliensis*, etc);  
*Penicillium* (e.g., *Penicillium marneffei*, etc);  
*Phialophora*;  
*Pneumocystis* (e.g., *Pneumocystis carinii*, etc);
- 25 *Pseudallescheria* (e.g., *Pseudallescheria boydii*, etc);  
*Rhizopus* (e.g., *Rhizopus microsporus* var. *rhizopodiformis*,  
*Rhizopus oryzae*, etc);  
*Saccharomyces* (e.g., *Saccharomyces cerevisiae*, etc);  
*Scopulariopsis*;
- 30 *Sporothrix* (e.g., *Sporothrix schenckii*, etc);  
*Trichophyton* (e.g., *Trichophyton mentagrophytes*, *Trichophyton rubrum*, etc);  
*Trichosporon* (e.g., *Trichosporon asahii*, *Trichosporon cutaneum*, etc).



The above fungi are well-known to cause various infection diseases in skin, eye, hair, nail, oral mucosa, gastrointestinal tract, bronchus, lung, endocardium, brain, meninges, urinary organ, vaginal protion, oral cavity, ophthalmus, systemic, kidney, bronchus, heart, external auditory canal, bone, nasal cavity, paranasal cavity, spleen, liver, hypodermal tissue, lymph doct, gastrointestine, articulation, muscle, tendon, interstitial plasma cell in lung, blood, and so on.

10 Therefore, the polypeptide compound (I) of the present invention are useful for preventing and treating various infectious diseases, such as dermatophytosis (e.g., trichophytosis, etc), pityriasis versicolor, candidiasis, cryptococcosis, geotrichosis, trichosporosis, aspergillosis, 15 penicilliosis, fusariosis, zygomycosis, sporotrichosis, chromomycosis, coccidioidomycosis, histoplasmosis, blastomycosis, paracoccidioidomycosis, pseudallescheriosis, mycetoma, mycotic keratitis, otomycosis, pneumocystosis, fungemia, and so on.

20 The combination use of azoles such as fluconazole, voriconazole, itraconazole, ketoconazole, miconazole, ER 30346 and SCH 56592; polyenes such as amphotericin B, nystatin, liposamal and lipid forms thereof such as Abelcet, AmBisome, and 25 Amphocil; purine or pyrimidine nucleotide inhibitors such as flucytosine; or polyxins such as nikkomycines, in particular nikkomycine Z or nikkomycine X; other chitin inhibitors; elongation factor inhibitors such as sordarin and analogs thereof; mannan inhibitors such as predamycin, 30 bactericidal/permeability-inducing (BPI) protein products such as XMP.97 or XMP.127; or complex carbohydrate antifungal agents such as CAN-296; or the combination use of immunosuppressant such as tacrolimus with the polypeptide compound (I) or a salt thereof is effective against above infectious diseases.

35

The pharmaceutical composition of the present invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the polypeptide compound (I) or a pharmaceutically acceptable salt thereof, as an active ingredient in admixture with an organic or inorganic carrier or excipient which is suitable for rectal; pulmonary (nasal or buccal inhalation); ocular; external (topical); oral administration; parenteral (including subcutaneous, intravenous and intramuscular) administrations; insufflation (including aerosols from metered dose inhalator); nebulizer; or dry powder inhalator.

The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers in a solid form such as granules, tablets, dragees, pellets, troches, capsules, or suppositories; creams; ointments; aerosols; powders for insufflation; in a liquid form such as solutions, emulsions, or suspensions for injection; ingestion; eye drops; and any other form suitable for use. And, if necessary, there may be included in the above preparation auxiliary substance such as stabilizing, thickening, wetting, emulsifying and coloring agents; perfumes or buffer; or any other commonly may be used as additives.

The polypeptide compound (I) or a pharmaceutically acceptable salt thereof is/are included in the pharmaceutical composition in an amount sufficient to produce the desired antimicrobial effect upon the process or condition of diseases.

For applying the composition to humans, it is preferable to apply it by intravenous, intramuscular, pulmonary, oral administration, eye drop administration or insufflation. While the dosage of therapeutically effective amount of the polypeptide compound (I) varies from and also depends upon the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.01-400 mg of the polypeptide compound (I) per kg weight of human being in the case of intramuscular administration, a daily dose of 0.1-20 mg of the

polypeptide compound (I) per kg weight of human being, in case of oral administration, a daily dose of 0.5-50 mg of the polypeptide compound (I) per kg weight of human being is generally given for treating or preventing infectious diseases.

- 5 Especially in case of the treatment of prevention of Pneumocystis carinii infection, the followings are to be noted.

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation form pressurized as powders which may be formulated and the powder compositions may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation aerosol, which may be formulated as a suspension or solution of compound in suitable propellants such as fluorocarbons or hydrocarbons.

- 15 Because of desirability to directly treat lung and bronchi, aerosol administration is a preferred method of administration. Insufflation is also a desirable method, especially where infection may have spread to ears and other body cavities.
- 20 Alternatively, parenteral administration may be employed using drip intravenous administration.

For administration by intravenous administration, the preferred pharmaceutical composition is the lyophilized form containing the polypeptide compound (I) or its pharmaceutically acceptable salt.

- 25 The amount of the polypeptide compound (I) or its pharmaceutically acceptable salt contained in the composition for a single unit dosage of the present invention is 0.1 to 400 mg, more preferably 1 to 200 mg, still more preferably 5 to 100 mg, specifically 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 75, 80, 85, 90, 95 and 100 mg.

The present invention further provides the following ones.

- 35 An article of manufacture, comprising packaging material

and the compound (I) identified in the above contained within said packaging material, wherein said the compound (I) is therapeutically effective for preventing or treating infectious diseases caused by pathogenic microorganism, and wherein said

5 packaging material comprises a label or a written material which indicates that said compound (I) can or should be used for preventing or treating infectious diseases caused by pathogenic microorganism.

- 10 A commercial package comprising the pharmaceutical composition containing the compound (I) identified in the above and a written matter associated therewith, wherein the written matter states that the compound (I) can or should be used for preventing or treating infectious diseases caused by pathogenic
- 15 microorganism.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

To a solution of 1-N-t-butyloxycarbonyl-4-hydroxypiperidine (5.0 g) in dimethylformamide (DMF) (25 ml) was portionwise added sodium hydride (60% in oil) (1.29 g) with stirring under ice-cooling. The mixture was successively stirred at ambient temperature for 30 minutes, stirred at 60°C for 1 hour and cooled with an ice bath. To the reaction mixture was added 1,5-dibromopentane (6.72 ml), and the mixture was stirred at ambient temperature for 3 hours. The reaction solution was poured into water (100 ml) and extracted twice with a mixture of ethyl acetate (80 ml) and n-hexane (30 ml). The extract was washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (5:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give 4-(5-bromopentyloxy)-1-N-t-butoxycarbonylpiperidine (2.44 g).

NMR (CDCl<sub>3</sub>, δ): 1.46 (9H, s), 1.50-1.70 (6H, m), 1.70-1.96 (4H, m), 3.00-3.15 (2H, m), 3.35-3.50 (5H, m), 3.70-3.90 (2H, m)

APCI MASS (m/z): 250 (M<sup>+</sup>-101)

Preparation 2

To a solution of 4-(5-bromopentyloxy)-1-N-t-butoxycarbonylpiperidine (2.44 g) in methanol (13 ml) was added 28% sodium methoxide methanol solution (14.2 ml), and the mixture was stirred under reflux for 4 hours. The reaction mixture was evaporated in vacuo. The resulting residue was chromatographed on silica gel (250 ml) eluting with a mixture of n-hexane and ethyl acetate (5:1 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give 4-(5-methoxypentyloxy)-1-N-t-butoxycarbonylpiperidine (1.97 g).

NMR (CDCl<sub>3</sub>, δ): 1.45 (9H, s), 1.45-1.95 (10H, m), 3.03 (1H,

dd,  $J=3.47$  and  $9.20\text{Hz}$ ),  $3.10$  (1H, dd,  $J=3.47$  and  $9.20\text{Hz}$ ),  $3.44$  (3H, s),  $3.34\text{--}3.50$  (5H, m),  $3.70\text{--}3.85$  (2H, m)

APCI MASS ( $m/z$ ): 202 ( $M^+$ -101)

5

### Preparation 3

To a solution of 4-(5-methoxypentyloxy)-1-N-t-butoxycarbonylpiperidine (1.97 g) in ethyl acetate (20 ml) was added 4N-hydrogen chloride ethyl acetate solution (16.3 ml), and the mixture was stirred at ambient temperature for 2 hours. The reaction mixture was evaporated in vacuo. The resulting residue was dissolved in a mixture of dichloromethane and methanol (10:1; 50 ml:5 ml). To this solution was added 1N-sodium hydroxide (5 ml) with stirring. The organic layer was separated and evaporated under reduced pressure to give 4-(5-methoxypentyloxy)-piperidine (0.62 g).

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.25-1.50 (2H, s), 1.50-1.75 (6H, m), 1.9-2.10 (2H, m), 2.70-2.90 (2H, m), 2.95-3.20 (2H, m), 3.33 (3H, s), 3.35-3.50 (5H, m)

APCI MASS ( $m/z$ ): 202 ( $M^+$ )

### Preparation 4

A solution of 4-fluorobenzonitrile (0.38 g), 4-(5-methoxypentyloxy)piperidine (0.62 g) and potassium carbonate (0.87 g) in DMF (8 ml) was stirred at  $90\text{--}95^\circ\text{C}$  for 6 hours. The reaction mixture was poured into water (50 ml) and extracted twice with a mixture of ethyl acetate and n-hexane (50ml:20 ml). The extracts were combined, washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (100 ml) eluting with a mixture of n-hexane and ethyl acetate (5:1 v/v - 2:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give 4-(5-methoxypentyloxy)-N-(4-cyanophenyl)piperidine (294 mg).

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.35-1.55 (2H, s), 1.55-1.75 (5H, m),

35

1.85-2.05 (2H, m), 3.13 (1H, dd, J=3.47 and 9.20Hz),  
3.17 (1H, dd, J=3.47 and 9.20Hz), 3.33 (3H, s),  
3.35-3.75 (8H, m), 6.85 (2H, d, J=9.01Hz), 7.47 (2H,  
d, J=8.96Hz)

5 APCI MASS (m/z): 303 ( $M^+$ )

#### Preparation 5

A solution of 4-(5-methoxypentyloxy)-N-(4-cyanophenyl)piperidine (294 mg) and thiosemicarbazide (0.68 g)  
10 in toluene (20 ml) and trifluoroacetic acid (10 ml) was stirred at 60-65°C for 7 hours. After cooling, the reaction mixture was poured into a mixture of water (100 ml) and ethyl acetate (200 ml) and adjusted to pH 10 with 1N-sodium hydroxide. The mixture was dissolved in a mixture of THF (50 ml) and methanol (10 ml).  
15 The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting precipitate was washed with isopropyl ether and dried in vacuo to give 2-amino-5-[4-[4-(5-methoxypentyloxy)-  
20 piperidin-1-yl]phenyl]-1,3,4-thiadiazole (1.29 g).

NMR ( $CDCl_3+CD_3OD$ ,  $\delta$ ): 1.30-1.50 (2H, m), 1.50-1.80 (6H, m),  
1.90-2.10 (2H, m), 2.9-3.10 (2H, m), 3.34 (3H, s),  
3.35-3.70 (7H, m), 6.93 (2H, d, J=8.91Hz), 7.63 (2H,  
d, J=8.83Hz)

25 APCI MASS (m/z): 377 ( $M^+$ )

#### Preparation 6

To a suspension of 2-amino-5-[4-[4-(5-methoxypentyloxy)piperidin-1-yl]phenyl]-1,3,4-thiadiazole  
30 (1.29 g) in ethanol (20 ml) was added ethyl 4-bromoacetylbenzoate (1.39 g) and stirred at reflux for 5 hours. The reaction mixture was cooled and poured into diisopropyl ether (IPE) (60 ml). The resulting precipitate was collected by filtration and dried. To a suspension of the precipitate in xylene (40 ml) was added  
35 trifluoroacetic acid (4 ml), and the mixture was stirred at

reflux (130°C) for 5 hours. The reaction mixture was cooled and poured into IPE (300 ml). The resulting precipitate was filtered and dried to give 4-[2-[4-[4-(5-methoxypropyloxy)piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid ethyl ester trifluoroacetic acid salt (2.01 g).

NMR (CDCl<sub>3</sub>, δ): 1.42 (3H, t, J=7.12Hz), 1.45-1.75 (6H, m), 1.85-2.10 (2H, m), 2.30-2.50 (2H, m), 3.36 (3H, s), 3.35-3.55 (5H, m), 3.60-3.80 (2H, m), 4.40 (2H, q, J=7.14Hz), 7.57 (2H, d, J=8.78 Hz), 7.84 (2H, d, J=8.40Hz), 7.91 (2H, d, J=8.79Hz), 8.13 (1H, s)

APCI MASS (m/z): 549 (M<sup>+</sup>+1)

#### Preparation 7

To a solution of 4-[2-[4-[4-(5-methoxypropyloxy)piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid ethyl ester trifluoroacetic acid salt (2.01 g) in a mixture of methanol (40 ml) and tetrahydrofuran (20 ml) was added 4N-NaOH (20 ml), and the mixture was refluxed for 6 hours. The reaction mixture was cooled, poured into water (200 ml) and adjusted to pH 2 with conc. HCl. The resulting precipitate was collected by filtration, washed in turn with water, isopropyl alcohol (30 ml) and IPE (50 ml) to give 4-[2-[4-[4-(5-methoxypropyloxy)piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid (1.28 g).

ESI MASS (m/z) (Negative): 519.2 (M<sup>+</sup>+1)

#### Preparation 8

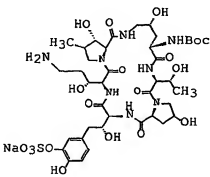
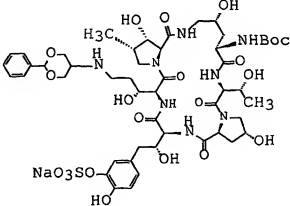
To a solution of 4-[2-[4-[4-(5-methoxypropyloxy)piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid (1.28 g) and 1-hydroxybenzotriazole (465 mg) in dichloromethane (50 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl) (943 mg), and the mixture was stirred overnight at ambient temperature. The reaction mixture was evaporated in vacuo. To the resulting precipitate was added water (50 ml) and filtered. The precipitate was washed with water and IPE (50 ml) and dried under



reduced pressure for 3 hours to give 4-[2-[4-[4-(5-methoxy-pentyloxy)piperidin-1-yl]phenyl]imidazo-[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid benzotriazol-1-yl ester (1.26 g).

- 5 IR (KBr): 1774.2, 1708.6, 1604.5, 1471.4, 1365.4,  
1230.4  $\text{cm}^{-1}$
- NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.30-1.80 (8H, m), 1.85-2.10 (2H, m),  
3.05-3.30 (2H, m), 3.33 (3H, s), 3.35-3.55 (4H, m),  
3.55-3.75 (2H, m), 6.94 (2H, d,  $J=8.94\text{Hz}$ ), 7.30-7.60  
10 (3H, m), 7.73 (2H, d,  $J=8.79\text{Hz}$ ), 8.00-8.20 (4H, m),  
8.30 (2H, d,  $J=8.46\text{Hz}$ )
- ESI MASS ( $m/z$ ) (Positive): 660.1 ( $M^+ + \text{Na}$ )

- The Starting Compounds used and the Object Compounds  
15 obtained in the following Preparation 9 is given in the table  
as below, in which the formula of the starting compound is in  
the upper column and the formula of the object compound are in  
the lower column, respectively.

Preparation No.	Formula
9	
	

### Preparation 9

To a solution of a mixture of the starting compound (9) (5.4 g), 2-oxo-1,3-diacetoxyp propane (4.85 g) and acetic acid (0.78 ml) in a mixture of methanol (80 ml) and dimethylformamide (40 ml) was added sodium cyanoborohydride (1.71 g) with stirring at ambient temperature, and the mixture was stirred at the same temperature overnight. The reaction mixture was concentrated in vacuo. To the resulting residue was added pH 6.86 standard buffer solution (100 ml) and acetonitrile (20 ml), and the solution was adjusted to pH 8.5 with 1N sodium hydroxide. The solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (400 ml) eluting in turn with water, 20% acetonitrile in water and 25% acetonitrile in water. The fractions containing

the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (9) (4.44 g).

IR (KBr): 1632, 1516, 1452, 1273, 1248  $\text{cm}^{-1}$

5 NMR (DMSO- $d_6$ ,  $\delta$ ): 0.98 (3H, d,  $J=6.88\text{Hz}$ ), 1.11 (3H, d,  $J=5.64\text{Hz}$ ), 1.36 (9H, s), 1.40-2.00 (6H, m), 2.50-2.95 (4H, m), 3.30-3.55 (2H, m), 3.65-4.45 (16H, m), 4.70-4.85 (2H, m), 5.36 (1H, s), 6.71 (1H, d,  $J=8.05\text{Hz}$ ), 6.77 (1H, d,  $J=8.29\text{Hz}$ ), 6.99 (1H, s), 7.30-7.45 (5H, m)

10 APCI MASS (m/z) (Positive): 1175.4 ( $\text{M}^+ + \text{Na}$ )

Elemental Analysis Calcd. for  $\text{C}_{50}\text{H}_{72}\text{N}_8\text{O}_{21}\text{S}\cdot 5\text{H}_2\text{O}$ :

C 46.80, H 6.52, N 8.73

Found: C 47.06, H 6.44, N 8.54

15

#### Preparation 10

To a solution of trans-4-methylcyclohexanol (4.55 g) in ethyl acetate (50 ml) were added successively triethylamine (7.22 ml) and methanesulfonyl chloride (3.38 ml) with stirring  
20 under ice-water bath. The mixture was stirred at the same temperature for 1 hour. To the reaction mixture were added ethyl acetate (50 ml), water (50 ml) and 1N hydrochloric acid (20 ml) with stirring. The organic layer was separated, washed successively with water, saturated aqueous sodium hydrogen  
25 carbonate, water and saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo to give trans-4-methylcyclohexyl methanesulfonate (8.36 g).

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.90 (3H, d,  $J=6.46\text{Hz}$ ), 0.95-1.70 (5H, m), 1.70-1.85 (2H, m), 2.00-2.20 (2H, m), 3.00 (3H, s),  
30 4.50-4.70 (1H, m)

#### Preparation 11

Piperazine (54.9 g) and methanol (5 ml) was stirred at  $120^\circ\text{C}$  to melt for 15 minutes. To the solution was dropwise added  
35 trans-4-methylcyclohexyl methanesulfonate (33.0 g) and the

mixture was stirred at the same temperature for 2 hours. After cooling, to the reaction mixture was added water (150 ml) and extracted three times with a mixture of ethyl acetate (100 ml) and THF (100 ml). The extracts were collected, dried over  
5 magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (600 ml) eluting with a mixture of dichloromethane, methanol and conc. ammonium hydroxide (4:1:0.1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give  
10 cis-1-(4-methylcyclohexyl)piperazine (17.76 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.92 (3H, d, J=6.96Hz), 1.40-1.65 (8H, m),  
1.65-1.85 (1H, m), 2.05-2.25 (1H, m), 2.45-2.60 (4H, m),  
2.85-2.95 (4H, m)

APCI MASS (m/z) (Positive): 183.2 (M<sup>+</sup>+1)

15

#### Preparation 12

A solution of ethyl 4-[4-(4-methylenecyclohexyl)-1-piperazinyl]benzoate (100 mg) and Iridium black (30 mg) in a mixture of t-butanol (1 ml) and methanol (2 ml) was stirred under  
20 atmospheric pressure of hydrogen for 4 hours. The catalyst was filtrated off and the filtrates were evaporated in vacuo. Ethyl 4-[cis-4-(4-methylcyclohexyl)-1-piperazinyl]benzoate and ethyl 4-[trans-4-(4-methylcyclohexyl)-1-piperazinyl]benzoate were obtained in the ratio 5:1-6:1 by thin-layer chromatography.

25

#### Preparation 13

To a suspension of 1-[4-[5-(4-iodophenyl)-1,3,4-thiadiazol-2-yl]phenyl]-4-(4-methylcyclohexyl)piperazine (2 g) in DMF (40 ml) was successively added ethyl formate (0.56 ml),  
30 dichlorobis(triphenylphosphine)palladium(II) (0.52 g) and 20% sodium ethoxide ethanol solution (4.43 ml) with stirring and the mixture was stirred at 40°C for 2 hours. The reaction mixture was added diisopropyl ether (600 ml). The resulting precipitate was collected by filtration. The precipitate was dissolved THF  
35 (200 ml), insoluble materials were filtered off and solution was

concentrated in vacuo. The resulting residue was washed with acetonitrile, and dried to give ethyl 4-[5-[4-[4-(4-methylcyclohexyl)-1-piperazinyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoate (1.07 g).

5 NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.93-0.96 (3H, m), 1.39-3.37 (18H, m), 4.42 (2H, q, J=7.1Hz), 6.96 (2H, d, J=8.9Hz), 7.87-8.17 (6H, m)

MASS (m/z): 491.4 (M<sup>+</sup>+1)

#### 10 Preparation 14

To a solution of methyl triphenylphosphonium bromide (13.7 g) in DMSO (140 ml) was added potassium tert-butoxide (4.31 g) under ice-cooling and the mixture was stirred for 1.5 hours at ambient temperature. After cooling, 1,4-

15 dioxaspiro[4,5]decan-8-one (5.0 g) was dropwise added to the solution under ice-cooling and then stirred for 1 hour at room temperature. The reaction mixture was poured into water (300 ml) and extracted twice with ethyl acetate (150 ml). The extracts were washed with saturated aqueous sodium chloride, dried over  
20 magnesium sulfate and evaporated in vacuo to give a residue. The residue was washed with a mixture of hexane and ethyl acetate (5:1 v/v) (300 ml). The resulting precipitates were collected and were chromatographed on silica gel (500 ml) eluting with a mixture of n-hexane and ethyl acetate (5:1 v/v). The fractions  
25 containing the desired compound were collected and evaporated under reduced pressure to give 8-methylene 1,4-dioxaspiro[4,5]decane (5.56 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.70 (4H, t, J=6.46Hz), 2.29 (4H, t, J=6.84Hz), 3.97 (4H, s), 4.67 (2H, s)

30

#### Preparation 15

A solution of 8-methylene 1,4-dioxaspiro[4,5]decane (5.55 g) in a mixture of acetone (60 ml) and water (4 ml) and p-toluenesulfonic acid monohydrate (1.37g) was stirred at ambient  
35 temperature overnight. To a solution was added p-

toluenesulfonic acid monohydrate (1.37 g) and the mixture was stirred at ambient temperature for 8 hours. Ethyl acetate (150 ml) was added to the reaction mixture and the solution was washed in turn with water, saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (150 ml) eluting with a mixture of n-hexane and ethyl acetate (9:1 v/v). The fraction containing the desired compound were collected and evaporated under reduced pressure to give 4-methylenecyclohexan-1-one (0.98 g). This compound was immediately used as the starting compound for the next step.

#### Preparation 16

To a solution of 1,4-dioxaspiro[4,5]decan-8-one (96.9 g) in methanol (1 l) was added portionwise sodium borohydride (46.9 g) under ice-cooling. After stirring for 3.5 hours under ice cooling, the reaction mixture was successively stirred for 3 hours at room temperature. Then the solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel eluting with a mixture of hexane and ethyl acetate (1:1). The eluted fractions containing the desired product were collected and evaporated in vacuo to give 1,4-dioxaspiro-[4,5]decan-8-ol (97.9 g).

NMR (CDCl<sub>3</sub>, δ): 1.4-2.0 (9H, m), 3.7-3.9 (1H, m), 3.95 (4H, s)

#### Preparation 17

To a solution of tert-butyl 4-(5-bromophenyloxy)-1-piperidinecarboxylate (12.98 g) in methanol (70 ml) was added 28% sodium methoxide methanol solution (37.8 ml) and the mixture was stirred under refluxing for 4 hours. After cooling, the reaction mixture was evaporated in vacuo. The resulting residue was chromatographed on silica gel (400 ml) eluting with a mixture of n-hexane and ethyl acetate (5:1 v/v). The fractions

containing the object compound were collected and evaporated under reduced pressure to give tert-butyl 4-(5-methoxypentyloxy)-1-piperidinecarboxylate (16.31 g). This compound was immediately used as the starting compound for the next step.

#### Preparation 18

A solution of ethyl 4-fluorobenzoate (2.30 g), 4-(4-(methoxybutyloxymethyl)piperidine trifluoroacetate (3.6 g) and potassium carbonate (4.73 g) in DMSO (40 ml) was stirred at 140-150°C for 4 hours. The reaction mixture was poured into water (150 ml) and extracted twice with ethyl acetate (80 ml). The extracts were collected, washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (2:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give ethyl 4-[4-(4-methoxybutyloxymethyl)-1-piperidyl]benzoate (2.76 g).

NMR (CDCl<sub>3</sub>, δ): 1.20-1.45 (5H, m), 1.50-1.70 (3H, m), 1.70-1.90 (3H, m), 2.84 (2H, dt, J=2.49 and J=12.8Hz), 3.28 (2H, d, J=6.01Hz), 3.33 (3H, s), 3.35-3.50 (4H, m), 3.75-3.90 (2H, m), 4.32 (2H, q, J=7.11Hz), 6.85 (2H, d, J=9.06Hz), 7.92 (2H, d, J=9.01 Hz)

APCI MASS (m/z) (Positive): 350.4 (M<sup>+</sup>+1)

#### Preparation 19

To a solution of tert-butyl 4-(5-(methoxypentyloxymethyl)-1-piperidinecarboxylate (1.75 g) in dichloromethane (50 ml) and anisole (4.22 ml) was added trifluoroacetic acid (8.55 ml) under ice-cooling and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was evaporated in vacuo and azeotropically distilled three times with toluene (30 ml) and dried in vacuo to give 4-(5-(methoxypentyloxymethyl)piperidine trifluoroacetate (7.30

g, crude oil). A solution of this compound (1.89 g), ethyl 4-fluorobenzoate (1.21 g), and potassium carbonate (2.30 g) in DMSO (20 ml) was stirred at 150°C for 4 hours. The reaction mixture was poured into water (100 ml) and extracted twice with ethyl acetate (80 ml). The extracts were collected, washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (2:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give ethyl 4-[4-(5-methoxypentyloxymethyl)-1-piperidyl]benzoate (1.21 g).

NMR (CDCl<sub>3</sub>, δ): 1.20-1.50 (6H, m), 1.50-1.70 (5H, m), 1.75-1.90 (3H, m), 2.84 (2H, dt, J=2.49 and 12.7Hz), 3.28 (2H, d, J=6.02Hz), 3.33 (3H, s), 3.39 (4H, q, J=6.57Hz), 3.75-3.95 (2H, m), 4.32 (2H, q, J=7.10Hz), 6.86 (2H, d, J=9.06Hz), 7.90 (2H, d, J=9.00Hz)

#### Preparation 20

A solution of methyl 6-chloronicotinate (25.4 g) and piperazine (38.3 g) in dimethylsulfoxide (125 ml) was heated at 100°C for 2 hours then cooled and diluted with water, followed by extraction with ethyl acetate (4x). The combined organic layers were washed with water then dried over magnesium sulfate, filtered and evaporated to give a crude product that was triturated with isopropyl ether-hexane to yield methyl 6-(1-piperazinyl)nicotinate (25 g) as a light yellow powder.

NMR (CDCl<sub>3</sub>, δ): 1.81 (1H, s), 2.94-3.01 (4H, m), 3.63-3.68 (4H, m), 3.87 (3H, s), 6.58 (1H, d, J=9Hz), 8.01 (1H, dd, J=2.4 and 9Hz), 8.79 (1H, d, J=2.4Hz)

ESI MASS (m/z): 222 (M<sup>+</sup>+1)

#### Preparation 21

A solution of tert-butyl-4-[4-(methoxycarbonyl)phenyl]-1-piperidinecarboxylate (3.95 g) in a mixture of methanol (80



ml), THF (40 ml) and 4N sodium hydroxide (30 ml) was stirred at 80°C for 2 hours. The reaction mixture was concentrated in vacuo. To a residue was added water (100 ml) and adjusted to pH 3 with 1N hydrochloric acid. The solution was extracted twice with a mixture of ethyl acetate (100 ml) and THF (50 ml). The extracts were dried over magnesium sulfate and evaporated in vacuo to give 4-[1-(tert-butoxycarbonyl)-4-piperidyl]benzoic acid (3.64g).

NMR (CDCl<sub>3</sub>, δ): 1.49 (9H, s), 1.50-1.90 (4H, m), 2.60-2.95 (3H, m), 4.10-4.30 (2H, m), 7.30 (2H, d, J=8.33Hz), 8.05 (2H, d, J=8.27Hz)

ESI MASS (m/z) (Negative): 304.1 (M<sup>+</sup>-1)

### Preparation 22

To a solution of 4-[1-(tert-butoxycarbonyl)-4-piperidyl]benzoic acid (3.64 g) and 1-hydroxybenzotriazole (2.73 g) in dichloromethane (40 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl) (4.56 g) and the mixture was stirred at ambient temperature for 3 hours. To the reaction mixture was added water (20 ml) and an organic layer was separated and washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. A solution of the resulting residue in THF (30 ml) was added to a solution of conc. ammonium hydroxide (10 ml) in THF (30 ml) at ambient temperature and the mixture was stirred at the same temperature for 1 hour. To a reaction mixture was added ethyl acetate (200 ml) and the organic layer was separated, washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The precipitate was chromatographed on silica gel (200 ml) eluting with a mixture of dichloromethane and methanol (9:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give tert-butyl 4-[4-(aminocarbonyl)phenyl]-1-piperidinecarboxylate (3.34 g).

NMR (CDCl<sub>3</sub>, δ): 1.48 (9H, s), 1.50-1.90 (4H, m), 2.60-2.95 (3H, m), 4.15-4.30 (2H, m), 5.75-6.25 (1H, broad m),

7.33 (2H, d,  $J=9.14\text{Hz}$ ), 7.76 (2H, d,  $J=8.28\text{Hz}$ )  
ESI MASS ( $m/z$ ) (Positive): 327.3 ( $M^+ + Na$ )

#### Preparation 23

- 5 To a solution of tert-butyl 4-[4-(aminocarbonyl)phenyl]-1-piperidinecarboxylate (3.34 g) in DMF (18 ml) was dropwise added phosphoryloxchloride (3.07 ml) keeping under  $10^\circ\text{C}$  with stirring and the mixture was stirred at ambient temperature for 10 minutes. The reaction mixture was poured into a mixture of saturated aqueous sodium carbonate (60 ml) and ice-water (250 ml) with stirring and extracted twice with a mixture of ethyl acetate (200 ml) and hexane (80 ml). The extract was washed twice with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (300 ml) eluting with a mixture of n-hexane and ethyl acetate (4:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give tert-butyl 4-(4-cyanophenyl)-1-piperidine carboxylate (3.13 g).
- 10 IR (KBr): 2227.4, 1699.0, 1677.8, 1608.3, 1504.2, 1423.2, 1369.2  $\text{cm}^{-1}$
- 15 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.48 (9H, s), 1.50-1.90 (4H, m), 2.60-2.95 (3H, m), 4.15-4.30 (2H, m), 7.30 (2H, d,  $J=8.26\text{Hz}$ ), 7.60 (2H, d,  $J=8.33\text{Hz}$ )
- 25 APCI MASS ( $m/z$ ) (Positive): 309.3 ( $M^+ + Na$ )

#### Preparation 24

- A mixture of cis-1-(4-methylcyclohexyl)piperazine (2.15 g), 4-fluorobenzonitrile (1.72 g) and potassium carbonate (4.89 g) in DMSO (25 ml) was stirred at  $140^\circ\text{C}$  for 4 hours. The reaction mixture was poured into water (150 ml) and extracted twice with ethyl acetate (150 ml). The extracts were collected, washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was
- 30 chromatographed on silica gel (200 ml) eluting with a mixture
- 35

of n-hexane and ethyl acetate (2:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give ethyl 4-[cis-4-(4-methylcyclohexyl)-1-piperazinyl]benzonitrile (2.81 g).

- 5        NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.93 (3H, d, J=6.87Hz), 1.40-1.80 (9H, m), 2.15-2.30 (1H, m), 2.60-2.70 (4H, m), 3.25-3.35 (4H, m), 6.86 (2H, d, J=9.06Hz), 7.48 (2H, d, J=9.04Hz)  
APCI MASS (m/z) (Positive): 284.3 (M<sup>+</sup>+1)

10    Preparation 25

- To a solution of 4-hydroxycyclohexylcyclohexane (25 g) in acetone (250 ml) was added dropwise with stirring 2.67N Jone's reagent (77 ml) at 0°C. The mixture was then stirred for 1 hour at 0°C. The organic layer was collected and evaporated. The reaction mixture was added to a mixture of water and diethyl ether. The organic layer was washed with water, sodium hydrogen carbonate solution and brine. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure
- 15    to give 4-cyclohexylcyclohexanone (19.57 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.8-1.4 (6H, m), 1.4-1.9 (8H, m), 1.9-2.15 (2H, m), 2.15-2.5 (4H, m)

MASS (m/z): 181 (M<sup>+</sup>+1)

25    Preparation 26

- A solution of oxalyl chloride (2.14 ml) in dichloromethane (80 ml) was cooled to -78°C in nitrogen atmosphere, and a solution of dimethylsulfoxide (6 ml) in dichloromethane (6 ml) was added slowly and stirred for 10 minutes at -78°C. To the reaction mixture was added a solution of 4'-methoxy-1,1'-bi(cyclohexyl)-4-ol (2.6 g) in dichloromethane (26 ml) slowly to maintain the reaction temperature and stirred for 2.5 hours at -40°C. To the reaction mixture was added triethylamine (12.4 ml) slowly. Then the reaction mixture allowed to warm to room
- 30    temperature. To the reaction mixture was added ammonium chloride
- 35

solution and ethyl acetate. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give 4'-methoxy-1,1'-bi(cyclohexyl)-4-one (1.62 g).

5 NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.9-2.5 (18H, m), 3.0-3.2 (1H, m), 3.35 (3H, s)

MASS (m/z): 233 (M<sup>+</sup>+1)

#### Preparation 27

10 A solution of 4-(4-hydroxyphenyl)cyclohexanone (5 g) and iodomethane (0.828 ml) in N,N-dimethylformamide (50 ml) was treated with potassium carbonate (4.36 g) at room temperature for 28 hours. Water was poured into the reaction mixture. And the resulting precipitate was collected by filtration and washed  
15 with isopropanol and diisopropyl ether to give 4-(4-methoxyphenyl)cyclohexanone (6.815 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.75-2.35 (4H, m), 2.4-2.6 (4H, m), 2.9-3.1 (1H, m), 3.80 (3H, s), 6.87 (2H, d, J=8.7Hz), 7.17 (2H, d, J=8.7Hz)

20 MASS (m/z): 227 (M<sup>+</sup>+23)

#### Preparation 28

To a solution of 4,4-dimethyl-2-cyclohexen-1-one (10 g) in ethanol (100 ml) was added 10% palladium on carbon (1 g), and  
25 hydrogen gas at atmosphere pressure for 4 hours. To the reaction mixture was filtered. The filtrate was concentrated by evaporation under reduced pressure to give 4,4-dimethylcyclohexanone (10.03 g).

30 NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.92 (3H, s), 1.10 (3H, s), 1.25-1.4 (2H, m), 1.5-1.75 (4H, m), 2.3-2.45 (2H, m)

MASS (m/z): 149 (M<sup>+</sup>+23)

#### Preparation 29

A mixture of cis-1-(4-methylcyclohexyl)piperazine (29.6 g),  
35 ethyl 4-fluorobenzoate (41.0 g) and potassium carbonate (67.3

g) in DMSO (300 ml) was stirred at 140°C for 9 hours. The reaction mixture was poured into water (1.2 l) and extracted twice with ethyl acetate (400 ml). The extracts were collected, washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (1 l) eluting with a mixture of n-hexane and ethyl acetate (2:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give ethyl 4-[cis-4-(4-methylcyclohexyl)-1-piperazinyl]benzoate (37.64 g).

NMR (CDCl<sub>3</sub>, δ): 0.93 (3H, d, J=6.87Hz), 1.36 (3H, t, J=7.11Hz), 1.40-1.80 (9H, m), 2.15-2.25 (1H, m), 2.60-2.70 (4H, m), 3.25-3.50 (4H, m), 4.32 (2H, q, J=7.11Hz), 6.86 (2H, d, J=8.94Hz), 7.92 (2H, d, J=8.87Hz)

ESI MASS (m/z) (Positive): 683.4 (2M<sup>+</sup>+Na), 331.3 (M<sup>+</sup>+1)

The following compounds [Preparations 30 and 31] were obtained according to a similar manner to that of Preparation 29.

#### Preparation 30

Ethyl 4-[4-(5-methoxypropyloxy)-1-piperidyl]benzoate

NMR (CDCl<sub>3</sub>, δ): 1.36 (3H, t, J=7.12Hz), 1.37-1.75 (8H, m), 1.85-2.05 (2H, m), 3.00-3.18 (2H, m), 3.33 (3H, s), 3.34-3.60 (5H, m), 3.60-3.75 (2H, m), 4.32 (2H, q, J=7.11Hz), 6.86 (2H, d, J=9.00Hz), 7.90 (2H, d, J=8.93Hz)

ESI MASS (m/z) (Positive): 372.3 (M<sup>+</sup>+Na)

#### Preparation 31

Ethyl 4-[4-(6-methoxyhexyloxy)-1-piperidyl]benzoate

NMR (CDCl<sub>3</sub>, δ): 1.3-1.8 (3H, m), 1.8-2.1 (12H, m), 3.0-3.2 (2H, m), 3.33 (3H, s), 3.3-3.5 (5H, m), 3.6-3.8 (2H, m), 4.32 (2H, q, J=7.1Hz), 6.86 (2H, d, J=9.1Hz),

7.8-8.0 (2H, m)

ESI MASS (m/z) (Positive): 364.33 ( $M^+$ +Na)

### Preparation 32

- 5 To a suspension of 4-[4-(4-methylcyclohexyl)-1-piperazinyl]benzohydrazide (12.48 g) and pyridine (11.7 ml) in THF (374 ml) was added 4-iodobenzoyl chloride (11 g) under ice-cooling and the mixture was stirred at the same temperature for 1 hour. The reaction mixture was added water (3700 ml). The  
10 resulting precipitate was collected by filtration and dried to give N'-(4-iodobenzoyl)-4-[4-(4-methylcyclohexyl)-1-piperazinyl]benzohydrazide (22.45 g).

- NMR (DMSO- $d_6$ ,  $\delta$ ): 0.88-0.92 (3H, m), 1.42-3.37 (18H, m),  
6.99 (2H, d,  $J=8.9$ Hz), 7.69 (2H, d,  $J=8.4$ Hz), 7.80 (2H,  
15 d,  $J=8.80$ Hz), 7.92 (2H, d,  $J=8.44$ Hz), 10.21 (1H, s),  
10.45 (1H, s)

MASS (m/z): 547 ( $M^+$ +1)

- The following compounds [Preparations 33 to 46] were  
20 obtained according to a similar manner to that of Preparation 32.

### Preparation 33

- Methyl 4-[2-[4-(4-methylenecyclohexyl)-1-  
25 piperazinyl]benzoyl]hydrazinocarbonyl]benzoate

IR (KBr): 3458, 3253, 2943, 2837, 1722, 1678, 1645, 1608,  
1510  $\text{cm}^{-1}$

- NMR (DSMO- $d_6$ ,  $\delta$ ): 1.10-1.50 (2H, m), 1.60-2.10 (4H, m),  
2.15-2.40 (2H, m), 2.50-2.70 (4H, m), 3.10-3.40 (4H,  
30 m), 3.80-4.00 (2H, m), 4.61 (1H, br s), 6.98 (2H, d,  
 $J=8.9$ Hz), 7.81 (2H, d,  $J=8.8$ Hz), 7.95 (4H, q,  $J=8.6$ Hz),  
10.26 (1H, s), 10.57 (1H, s)

MASS (m/z): 479 ( $M^+$ +1), 478 (M), 477 ( $M^+$ -1)

- 35 Preparation 34

Methyl 4-[2-[4-[4-(4-phenylcyclohexyl)-1-piperazinyl]benzoyl]hydrazinocarbonyl]benzoate

APCI MASS (m/z): 541.4 ( $M^+ + 1$ )

5 Preparation 35

Methyl 4-[5-[4-(4-phenylcyclohexyl)-1-piperazinyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoate

APCI MASS (m/z): 539.4 ( $M^+ + 1$ )

10 Preparation 36

Methyl 4-[2-[4-[4-(cyclohexylmethyl)-1-piperazinyl]benzoyl]hydrazinocarbonyl]benzoate

15 NMR (DMSO- $d_6$ ,  $\delta$ ): 0.7-1.0 (2H, m), 1.1-1.8 (9H, m), 2.12 (2H, d,  $J=7.1$ Hz), 2.4-2.5 (4H, m), 3.2-3.4 (4H, m), 3.90 (3H, s), 6.98 (2H, d,  $J=9$ Hz), 7.81 (2H, d,  $J=9$ Hz), 8.02 (2H, d,  $J=8.7$ Hz), 8.09 (2H, d,  $J=8.7$ Hz), 10.26 (1H, s), 10.58 (1H, s)

APCI MASS (m/z) (Positive): 479.4 ( $M^+ + 1$ )

20 Preparation 37

4-[2-[4-[4-[4-(7-Methoxyheptyloxy)cyclohexyl]-1-piperazinyl]benzoyl]hydrazinocarbonyl]benzoate

IR (Neat): 2933, 2858, 1724, 1682, 1645, 1608, 1279, 1242, 1113  $\text{cm}^{-1}$

25 NMR (DSMO- $d_6$ ,  $\delta$ ): 1.0-2.1 (18H, m), 2.2-2.4 (1H, m), 2.52 (4H, m), 3.0-3.5 (9H, m), 3.20 (3H, s), 3.90 (3H, s), 6.9-7.1 (2H, m), 7.7-7.9 (2H, m), 8.0-8.2 (4H, m), 10.26 (1H, s), 10.58 (1H, s)

ESI MASS (m/z) (Positive): 609.5 ( $M^+ + 1$ )

30

Preparation 38

4-[2-[4-[4-[4-(8-Methoxyoctyloxy)cyclohexyl]-1-piperazinyl]benzoyl]hydrazinocarbonyl]benzoate

35 IR (Neat): 2931, 2856, 1724, 1680, 1647, 1608, 1520, 1281, 1240, 1113  $\text{cm}^{-1}$

NMR (DSMO-d<sub>6</sub>,  $\delta$ ): 1.0-2.1 (20H, m), 2.2-2.4 (1H, m), 2.5-2.7 (4H, m), 3.0-3.6 (9H, m), 3.21 (3H, s), 3.90 (3H, s), 6.9-7.1 (2H, m), 7.7-7.9 (2H, m), 8.0-8.2 (4H, m), 10.26 (1H, s), 10.58 (1H, s)

5 ESI MASS (m/z) (Positive): 623.5 ( $M^+$ +1)

#### Preparation 39

Methyl 4-[2-[4-[4-(5-methoxypropyloxy)-1-piperidyl]benzoyl]hydrazinocarbonyl]benzoate

10 NMR (DSMO-d<sub>6</sub>,  $\delta$ ): 1.20-1.60 (8H, m), 1.80-1.95 (2H, m), 2.95-3.20 (2H, m), 3.21 (3H, s), 3.25-3.80 (7H, m), 3.90 (3H, s), 6.99 (2H, d,  $J=8.92\text{Hz}$ ), 7.80 (2H, d,  $J=8.76\text{Hz}$ ), 8.03 (2H, d,  $J=8.56\text{Hz}$ ), 8.09 (2H, d,  $J=8.54\text{Hz}$ ), 10.24 (1H, s), 10.57 (1H, s)

15 ESI MASS (m/z) (Positive): 520.3 ( $M^+$ +Na)

#### Preparation 40

Methyl 4-[2-[4-[4-(6-methoxyhexyloxy)-1-piperidyl]benzoyl]hydrazinocarbonyl]benzoate

20 NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.3-2.1 (12H, m), 3.0-3.2 (2H, m), 3.33 (3H, s), 3.3-3.5 (5H, m), 3.5-3.7 (2H, m), 3.94 (3H, s), 6.83 (2H, d,  $J=9.0\text{Hz}$ ), 7.74 (2H, d,  $J=8.9\text{Hz}$ ), 7.90 (2H, d,  $J=8.5\text{Hz}$ ), 8.04 (2H, d,  $J=8.5\text{Hz}$ ), 9.52 (1H, d,  $J=5.0\text{Hz}$ ), 10.11 (1H, d,  $J=5.2\text{Hz}$ )

25 (+) APCI MASS (m/z) (Positive): 512.40 ( $M^+$ +1)

#### Preparation 41

Methyl 4-[2-[4-[4-(4-methoxybutoxymethyl)-1-piperidyl]benzoyl]hydrazinocarbonyl]benzoate

30 NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.2-1.9 (9H, m), 2.7-2.9 (2H, m), 3.2-3.5 (6H, m), 3.33 (3H, s), 3.8-4.0 (2H, m), 3.94 (3H, s), 6.84 (2H, d,  $J=9.0\text{Hz}$ ), 7.74 (2H, d,  $J=8.9\text{Hz}$ ), 7.91 (2H, d,  $J=8.4\text{Hz}$ ), 8.06 (2H, d,  $J=8.5\text{Hz}$ ), 9.40 (1H, d,  $J=5.0\text{Hz}$ ), 9.96 (1H, d,  $J=5.6\text{Hz}$ )

35 (+) APCI MASS (m/z) (Positive): 497.93 ( $M^+$ +1)



Preparation 42

Methyl 4-[2-[4-[4-(5-methoxypentyloxymethyl)-1-piperidyl]benzoyl]hydrazinocarbonyl]benzoate

5 NMR (CDCl<sub>3</sub>, δ): 1.2-1.9 (11H, m), 2.7-2.9 (2H, m), 3.2-3.5 (6H, m), 3.33 (3H, s), 3.8-4.0 (2H, m), 3.94 (3H, s), 6.83 (2H, d, J=9.0Hz), 7.74 (2H, d, J=8.8Hz), 7.90 (2H, d, J=8.4Hz), 8.05 (2H, d, J=8.4Hz), 9.47 (1H, d, J=4.9Hz), 10.06 (1H, d, J=5.3Hz)

10 ESI MASS (m/z) (Positive): 534.4 (M<sup>+</sup>+Na)

Preparation 43

Methyl 4-[2-[6-[4-(4-methylcyclohexyl)-1-piperazinyl-3-pyridyl]carbonyl]hydrazinocarbonyl]benzoate

15 NMR (CDCl<sub>3</sub>, δ): 0.94 (3H, d, J=6.9Hz), 1.4-2.0 (9H, m), 2.1-2.3 (1H, m), 2.6-2.7 (4H, m), 3.6-3.8 (4H, m), 3.96 (3H, s), 6.62 (1H, d, J=9.1Hz), 7.8-8.0 (3H, m), 8.13 (2H, d, J=8.4Hz), 8.69 (1H, d, J=2.3Hz)

(+) APCI MASS (m/z) (Positive): 480.27 (M<sup>+</sup>+1)

20

Preparation 44

Methyl 4-[2-[6-[4-(4-methylcyclohexyl)-1-piperazinyl-3-pyridyl]carbonyl]hydrazinocarbonyl]benzoate

25 NMR (CDCl<sub>3</sub>, δ): 0.8-2.0 (12H, m), 2.2-2.4 (1H, m), 2.6-2.8 (4H, m), 3.6-3.8 (4H, m), 3.96 (3H, s), 6.62 (1H, d, J=9.2Hz), 7.8-8.0 (3H, m), 8.14 (2H, d, J=8.5Hz), 8.69 (1H, d, J=2.3Hz)

(+) APCI MASS (m/z) (Positive): 480.20 (M<sup>+</sup>+1)

30 Preparation 45

Methyl 4-[2-[6-[4-(4-ethylcyclohexyl)-1-piperazinyl-3-pyridyl]carbonyl]hydrazinocarbonyl]benzoate

35 NMR (CDCl<sub>3</sub>, δ): 0.8-1.0 (5H, m), 1.2-2.0 (9H, m), 2.1-2.3 (1H, m), 2.5-2.7 (4H, m), 3.6-3.8 (4H, m), 3.96 (3H, s), 6.62 (1H, d, J=9.1Hz), 7.8-8.0 (3H, m), 8.13 (2H,

d,  $J=8.3\text{Hz}$ ), 8.6-8.7 (1H, m)

(+) APCI MASS (m/z) (Positive): 494.20 ( $M^++1$ )

#### Preparation 46

5 Methyl 4-[2-[6-[4-(4-ethylcyclohexyl)-1-piperazinyl]-3-pyridyl]carbonyl]hydrazinocarbonyl]benzoate

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.8-2.0 (14H, m), 2.2-2.4 (1H, m), 2.6-2.8 (4H, m), 3.6-3.8 (4H, m), 3.96 (3H, s), 6.63 (1H, d,  $J=9.2\text{Hz}$ ), 7.8-8.0 (3H, m), 8.0-8.2 (2H, m), 8.6-8.7 (1H, m)

10

(+) APCI MASS (m/z) (Positive): 494.20 ( $M^++1$ )

#### Preparation 47

A suspension of N'-(4-iodobenzoyl)-4-[4-(4-methylcyclohexyl)-1-piperazinyl]benzohydrazide (22.95 g) in pyridine (459 ml) was treated with phosphorus pentasulfide (11.2 g) and stirred at  $120^\circ\text{C}$  for 2.5 hours. The reaction mixture was added a solution of sodium hydroxide (510 g) in water (9200 ml). The resulting precipitate was collected, washed with acetone. 20 The powder was recrystallized from THF (800 ml) and dried to give 1-[4-[5-(4-iodophenyl)-1,3,4-thiadiazol-2-yl]phenyl]-4-(4-methylcyclohexyl)piperazine (16.42 g).

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.93-0.96 (3H, m), 1.47-3.36 (18H, m), 6.95 (2H, d,  $J=9.0\text{Hz}$ ), 7.68-7.90 (6H, m)

25

MASS (m/z): 545 ( $M^++1$ )

The following compounds [Preparations 48 to 55] were obtained according to a similar manner to that of Preparation 47.

30

#### Preparation 48

Methyl 4-[5-[4-[4-(cyclohexylmethyl)-1-piperazinyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoate

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.8-1.05 (2H, m), 1.1-2.0 (9H, m), 2.22 (2H, d,  $J=7\text{Hz}$ ), 2.58 (4H, br s), 3.33-3.38 (4H, m), 3.96

35

(3H, s), 6.96 (2H, d, J=9Hz), 7.89 (2H, d, J=9Hz), 8.06  
(2H, d, J=8.6Hz), 8.15 (2H, d, J=8.6Hz)

APCI MASS (m/z) (Positive): 477.47 ( $M^+ + 1$ )

5 Preparation 49

Methyl 4-[5-[4-[4-(6-methoxyhexyloxy)-1-  
piperidyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoate

10 NMR ( $CDCl_3$ ,  $\delta$ ): 1.3-2.1 (12H, m), 3.0-3.2 (2H, m), 3.33 (3H,  
s), 3.3-3.6 (5H, m), 3.6-3.8 (2H, m), 3.96 (3H, s),  
6.96 (2H, d, J=8.9Hz), 7.88 (2H, d, J=8.6Hz), 8.06 (2H,  
d, J=8.6Hz), 8.15 (2H, d, J=8.6Hz)  
(+) APCI MASS (m/z) (Positive): 510.47 ( $M^+ + 1$ )

Preparation 50

15 Methyl 4-[5-[4-[4-(4-methoxybutoxymethyl)-1-  
piperidyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoate

20 NMR ( $CDCl_3$ ,  $\delta$ ): 1.2-2.0 (9H, m), 2.8-3.0 (2H, m), 3.3-3.5  
(6H, m), 3.34 (3H, s), 3.8-4.0 (2H, m), 3.96 (3H, s),  
6.95 (2H, d, J=9.0Hz), 7.88 (2H, d, J=8.9Hz), 8.0-  
8.2 (4H, m)  
(+) APCI MASS (m/z) (Positive): 496.27 ( $M^+ + 1$ )

Preparation 51

25 Methyl 4-[5-[4-[4-(5-methoxypentyloxymethyl)-1-  
piperidyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoate

30 NMR ( $CDCl_3$ ,  $\delta$ ): 1.2-2.0 (11H, m), 2.7-2.9 (2H, m), 3.2-3.5  
(6H, m), 3.34 (3H, s), 3.8-4.0 (2H, m), 3.96 (3H, s),  
6.95 (2H, d, J=9.0Hz), 7.88 (2H, d, J=8.9Hz), 8.0-  
8.2 (4H, m)  
(+) APCI MASS (m/z) (Positive): 510.40 ( $M^+ + 1$ )

Preparation 52

35 Methyl 4-[5-[6-[4-(4-methylcyclohexyl)-1-piperazinyl]-  
3-pyridyl]-1,3,4-thiadiazol-2-yl]benzoate

NMR ( $CDCl_3$ ,  $\delta$ ): 0.95 (3H, d, J=6.9Hz), 1.4-1.8 (9H, m),

2.1-2.3 (1H, m), 2.6-2.8 (4H, m), 3.6-3.8 (4H, m), 3.96 (3H, s), 6.72 (1H, d, J=9.1Hz), 8.0-8.2 (5H, m), 8.71 (1H, d, J=2.4Hz)

(+) APCI MASS (m/z) (Positive): 478.13 ( $M^+ + 1$ )

5

#### Preparation 53

Methyl 4-[5-[6-[4-(4-methylcyclohexyl)-1-piperazinyl]-3-pyridyl]-1,3,4-thiadiazol-2-yl]benzoate

10 NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.8-2.0 (12H, m), 2.2-2.4 (1H, m), 2.6-2.8 (4H, m), 3.6-3.8 (4H, m), 3.96 (3H, s), 6.72 (1H, d, J=9.0Hz), 8.0-8.2 (5H, m), 8.71 (1H, d, J=2.3Hz)

ESI MASS (m/z) (Positive): 478.3 ( $M^+ + 1$ )

#### Preparation 54

15 Methyl 4-[5-[6-[4-(4-ethylcyclohexyl)-1-piperazinyl]-3-pyridyl]-1,3,4-thiadiazol-2-yl]benzoate

20 NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.8-1.0 (5H, m), 1.2-1.9 (9H, m), 2.2-2.4 (1H, m), 2.6-2.8 (4H, m), 3.6-3.8 (4H, m), 3.96 (3H, s), 6.72 (1H, d, J=9.1Hz), 8.0-8.2 (5H, m), 8.71 (1H, d, J=2.3Hz)

(+) APCI MASS (m/z) (Positive): 492.13 ( $M^+ + 1$ )

#### Preparation 55

25 Methyl 4-[5-[6-[4-(4-ethylcyclohexyl)-1-piperazinyl]-3-pyridyl]-1,3,4-thiadiazol-2-yl]benzoate

NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.8-2.0 (14H, m), 2.2-2.4 (1H, m), 2.6-2.8 (4H, m), 3.6-3.8 (4H, m), 3.96 (3H, s), 6.72 (1H, d, J=8.9Hz), 8.0-8.2 (5H, m), 8.71 (1H, d, J=2.4Hz)

(+) APCI MASS (m/z) (Positive): 492.13 ( $M^+ + 1$ )

30

#### Preparation 56

To a mixture of ethyl 4-(piperazinyl)benzoate (2.00 g) and 4-methylenecyclohexan-1-one (0.98 g) in a mixture of methanol (40 ml) and acetic acid (1.47 ml) was portionwise added sodium cyanoborohydride (644 mg) with stirring under ice-cooling and

35

the mixture was stirred at ambient temperature overnight. To the reaction mixture was added water (200 ml) and the mixture was adjusted to pH 8-9 with saturated aqueous sodium hydrogen carbonate. The resulting precipitates were collected and chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (2:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give ethyl 4-[4-(4-methylenecyclohexyl)-1-piperazinyl]benzoate (1.39 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.36 (3H, t, J=7.12Hz), 1.39-1.50 (2H, m), 1.85-2.15 (4H, m), 2.30-2.60 (3H, m), 2.65-2.75 (4H, m), 3.25-3.35 (4H, m), 4.32 (2H, q, J=7.12Hz), 4.63 (2H, s), 6.85 (2H, d, J=9.08Hz), 7.92 (2H, d, J=9.04Hz)  
ESI MASS (m/z) (Positive): 329.4 (M<sup>+</sup>+1)

The following compounds [Preparations 57 to 63] were obtained according to a similar manner to that of Preparation 56.

#### Preparation 57

Ethyl 4-[4-(4-phenylcyclohexyl)-1-piperazinyl]benzoate  
NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.36 (3H, t, J=7.1Hz), 1.40-2.12 (8H, m), 2.31 (1H, br), 2.62-2.67 (4H, m), 3.32-3.37 (4H, m), 3.6-3.8 (1H, m), 4.33 (2H, q, J=7.1Hz), 6.87 (2H, d, J=9Hz), 7.1-7.35 (5H, m), 7.92 (2H, d, J=9Hz)  
APCI MASS (m/z) (Positive): 393.33 (M<sup>+</sup>+1)

#### Preparation 58

Ethyl 4-[4-(cyclohexylmethyl)-1-piperazinyl]benzoate  
NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.75-1.00 (2H, m), 1.36 (3H, t, J=7.1Hz), 1.10-1.82 (9H, m), 2.17 (2H, d, J=7.1Hz), 2.50-2.55 (4H, m), 3.29-3.34 (4H, m), 4.32 (2H, q, J=7.1Hz), 6.85 (2H, d, J=9Hz), 7.92 (2H, d, J=9Hz)  
APCI MASS (m/z) (Positive): 331.4 (M<sup>+</sup>+1)

Preparation 59

Ethyl 4-[4-[4-(7-methoxyheptyloxy)cyclohexyl]-1-piperazinyl]benzoate

IR (Neat): 1707, 1606, 1518, 1452, 1389, 1367, 1282, 1236,  
1188, 1119, 1107  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.2-2.2 (21H, m), 2.2-2.4 (1H, m), 2.7-2.8 (4H, m), 3.33 (3H, s), 3.1-3.8 (9H, m), 4.32 (2H, q,  $J=7.1\text{Hz}$ ), 6.86 (2H, d,  $J=9.0\text{Hz}$ ), 7.92 (2H, d,  $J=9.0\text{Hz}$ )

(+) AOCU MASS ( $m/z$ ) (Positive): 461.53 ( $M^+ + 1$ )

Preparation 60

Ethyl 4-[4-[4-(8-methoxyoctyloxy)cyclohexyl]-1-piperazinyl]benzoate

IR (Neat): 2933, 2856, 1705, 1608, 1516, 1454, 1282, 1238,  
1111  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.2-2.2 (23H, m), 2.2-2.4 (1H, m), 2.6-2.8 (4H, m), 3.1-3.5 (9H, m), 3.33 (3H, s), 4.32 (2H, q,  $J=7.1\text{Hz}$ ), 6.86 (2H, d,  $J=9.0\text{Hz}$ ), 7.92 (2H, d,  $J=9.0\text{Hz}$ )

ESI MASS ( $m/z$ ) (Positive): 475.5 ( $M^+ + 1$ )

Preparation 61

Methyl 6-[4-(cis-4-methylcyclohexyl)-1-piperazinyl]nicotinate

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.94 (3H, d,  $J=6.9\text{Hz}$ ), 1.40-1.82 (9H, m), 2.16-2.26 (1H, m), 2.59-2.65 (4H, m), 3.65-3.71 (4H, m), 3.86 (3H, s), 6.58 (1H, d,  $J=9\text{Hz}$ ), 8.00 (1H, dd,  $J=2.4$  and  $9\text{Hz}$ ), 8.79 (1H, d,  $J=2.4\text{Hz}$ )

API-ES MASS ( $m/z$ ) (Positive): 318.3 ( $M^+ + 1$ )

Methyl 6-[4-(trans-4-methylcyclohexyl)-1-piperazinyl]nicotinate

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.88 (3H, d,  $J=6.4\text{Hz}$ ), 0.90-1.40 (4H, m), 1.70-1.95 (5H, m), 2.20-2.35 (1H, m), 2.63-2.68 (4H, m), 3.65-3.70 (4H, m), 3.86 (3H, s), 6.57 (1H, d,  $J=9\text{Hz}$ ), 7.99 (1H, dd,  $J=2.4$  and  $9\text{Hz}$ ), 8.78 (1H, d,

J=2.4Hz)

API-ES MASS (m/z) (Positive): 318.3 ( $M^+ + 1$ )

#### Preparation 62

- 5 Methyl 6-[4-(cis-4-ethylcyclohexyl)-1-piperazinyl]nicotinate

NMR ( $CDCl_3$ ,  $\delta$ ): 0.87 (3H, t, J=7.3Hz), 1.25-1.67 (11H, m),  
2.20-2.30 (1H, m), 2.59-2.64 (4H, m), 3.65-3.70 (4H,  
m), 3.86 (3H, s), 6.58 (1H, d, J=9.1Hz), 8.00 (1H, dd,  
10 J=2.4 and 9.1Hz), 8.79 (1H, d, J=2.4Hz)

API-ES MASS (m/z) (Positive): 332.4 ( $M^+ + 1$ )

Methyl 6-[4-(trans-4-ethylcyclohexyl)-1-piperazinyl]nicotinate

- 15 NMR ( $CDCl_3$ ,  $\delta$ ): 0.87 (3H, t, J=7.5Hz), 0.91-1.40 (5H, m),  
1.6-2.0 (6H, m), 2.64-2.69 (4H, m), 3.66-3.71 (4H, m),  
3.86 (3H, s), 6.57 (1H, d, J=9Hz), 8.00 (1H, dd, J=2.3  
and 9Hz), 8.79 (1H, d, J=2.3Hz)

API-ES MASS (m/z) (Positive): 332.4

20

#### Preparation 63

4-(1-Cyclohexyl-4-piperidyl)benzonitrile

IR (KBr): 2927, 2852, 2222, 1605, 1504, 1450  $cm^{-1}$

- 25 NMR ( $DMSO-d_6$ ,  $\delta$ ): 1.0-2.0 (14H, m), 2.2-2.7 (4H, m), 2.8-3.1  
(2H, m), 7.45 (2H, d, J=8.3Hz), 7.75 (2H, d, J=8.3Hz)

(+) APCI MASS (m/z): 269.33 ( $M^+ + 1$ )

#### Preparation 64

- A mixture of 7-bromo-1-heptanol (25 g) and sodium methoxide,  
30 28% solution in methanol (37 ml) in methanol (250 ml) was stirred  
for 7 hours at 90°C. After being cooled to room temperature,  
the solvent was evaporated in vacuo. The residue was purified  
by column chromatography on silica gel eluting with a mixture  
of dichloromethane and methanol (100:1-25:1). The eluted  
35 fractions containing the desired product were collected and

evaporated in vacuo to give 7-methoxy-1-heptanol (18.2 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.2-1.7 (10H, m), 3.33 (3H, s), 3.3-3.4 (2H, m), 3.5-3.7 (2H, m)

- 5        The following compound was obtained according to a similar manner to that of Preparation 64.

Preparation 65

8-Methoxy-1-octanol

- 10        NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.2-1.7 (12H, m), 3.33 (3H, s), 3.3-3.4 (2H, m), 3.5-3.7 (2H, m)

Preparation 66

- To a mixture of 7-methoxy-1-heptanol (18.1 g) and p-toluenesulfonyl chloride (28.4 g) in dichloromethane (180 ml) was added triethylamine. After stirring for 27.5 hours at room temperature, the solvent was evaporated in vacuo. Then the residue was poured into a mixture of ethyl acetate and water. The organic layer was successively washed with water and brine and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel eluting with a mixture of hexane and ethyl acetate (8:1-5:1). The eluted fractions containing the desired product were collected and evaporated in vacuo to give 7-methoxyheptyl 4-methylbenzenesulfonate (28.5 g).
- 15  
20  
25

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.1-1.7 (10H, m), 2.45 (3H, s), 3.3-3.4 (5H, m), 4.02 (2H, t, J=6.5Hz), 7.3-7.4 (2H, m), 7.7-7.8 (2H, m)

ESI MASS (m/z) (Positive): 323.3 (M<sup>+</sup>+Na)

30

The following compound was obtained according to a similar manner to that of Preparation 66.

Preparation 67

- 35        8-Methoxyoctyl 4-methylbenzenesulfonate



NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.1-1.7 (12H, m), 2.45 (3H, s), 3.3-3.4 (5H, m), 4.01 (2H, d,  $J=6.5\text{Hz}$ ), 7.3-7.4 (2H, m), 7.7-7.9 (2H, m)

ESI MASS ( $m/z$ ) (Positive): 337.2 ( $M^+ + \text{Na}$ )

5

#### Preparation 68

A mixture of 8-(7-methoxyheptyloxy)-1,4-dioxaspiro[4.5]decane (9.8 g) and 3N aqueous hydrochloric acid (34 ml) in tetrahydrofuran (68 ml) was stirred for 25.5 hours at room temperature. The solvent was evaporated in vacuo and the residue was poured into a mixture of ethyl acetate and water. Then the solution was adjusted to pH 9 with potassium carbonate. The organic layer was successively washed with water and brine and dried over magnesium sulfate. The solvent was evaporated in vacuo to give 4-(7-methoxyheptyloxy)cyclohexanone (8.34 g).

15

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.2-2.4 (16H, m), 2.5-2.7 (2H, m), 3.33 (3H, s), 3.3-3.5 (4H, m), 3.6-3.8 (1H, m)

ESI MASS ( $m/z$ ) (Positive): 265.4 ( $M^+ + \text{Na}$ )

20

The following compound was obtained according to a similar manner to that of Preparation 68.

#### Preparation 69

4-(8-Methoxyoctyloxy)cyclohexanone

25

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.2-2.4 (18H, m), 2.5-2.7 (2H, m), 3.33 (3H, s), 3.3-3.5 (4H, m), 3.6-3.8 (1H, m)

ESI MASS ( $m/z$ ) (Positive): 279.3 ( $M^+ + \text{Na}$ )

#### Preparation 70

To a solution of tert-butyl 4-[4'-(methoxycarbonyl)-1,1'-biphenyl-4-yl]-1-piperazinecarboxylate (4.5 g) and anisole (6.17 ml) in dichloromethane (45 ml) was added dropwise with stirring trifluoroacetic acid (22.5 ml) at 0°C. The mixture was then stirred for 2 hours at room temperature. To the reaction mixture was added water. The resulting precipitate was collected

35

by filtration and washed with isopropanol and diisopropyl ether to give methyl 4'-(1-piperazinyl)-1,1'-biphenyl-4-carboxylate trifluoroacetate (4.13 g).

5 NMR (CDCl<sub>3</sub>,  $\delta$ ): 3.15-3.55 (8H, m), 3.87 (3H, s), 7.11 (2H, d, J=8.8Hz), 7.69 (2H, d, J=8.7Hz), 7.79 (2H, d, J=8.4Hz), 8.00 (2H, d, J=8.4Hz), 8.84 (2H, br s)  
MASS (m/z) (Positive): 297 (M<sup>+</sup>+1)

The following compounds [Preparation 71 to 73] were  
10 obtained according to a similar manner to that of Preparation 70.

Preparation 71

15 4-(5-Methoxypropyloxy)-1-piperidine trifluoroacetate

This compound was immediately used as the starting compound for the next step.

Preparation 72

20 4-(6-Methoxyhexyloxy)piperidine

This compound was immediately used as the starting compound for the next step.

25 Preparation 73

4-(4-Piperidyl)benzonitrile

IR (KBr): 2937, 2227, 1684, 1608, 1541, 1504, 1450, 1419, 1201, 1134, 1014, 835 cm<sup>-1</sup>

30 NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 1.4-1.8 (4H, m), 2.5-2.8 (3H, m), 3.0-3.1 (2H, m), 7.4-7.5 (2H, m), 7.7-7.8 (2H, m)  
(+) APCI MASS (m/z): 187.27 (M<sup>+</sup>+1)

Preparation 74

35 To an ice cooled solution of 1-methoxy-bicyclohexyl-4-one (0.9 g) and methyl 4'-(1-piperazinyl)-1,1'-biphenyl-4-

carboxylate trifluoroacetate (2.11 g) in a mixed solvent of methanol (18 ml), tetrahydrofuran (14 ml) and acetic acid (0.735 ml) was added sodium cyanoborohydride (296 mg) in a stream of nitrogen. The mixture was stirred at room temperature for 5 hours.

5 The reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate solution. The resulting precipitate collected by filtration, washed with water, isopropyl alcohol and diisopropyl ether, then dried to give methyl 4'-[4-[cis-1-methoxy-1,1'-bi(cyclohexyl)-4-yl]-1-piperazinyl]-1,1'-

10 biphenyl-4-carboxylate and 4'-[4-[trans-1-methoxy-1,1'-bi(cyclohexyl)-4-yl]-1-piperazinyl]-1,1'-biphenyl-4-carboxylate (444 mg).

4'-[4-[Cis-1-methoxy-1,1'-bi(cyclohexyl)-4-yl]-1-

15 piperazinyl]-1,1'-biphenyl-4-carboxylate

NMR (CDCl<sub>3</sub>, δ): 0.8-1.9 (19H, m), 2.15-2.4 (1H, m), 2.7-2.9 (4H, m), 3.11 (3H, s), 3.2-3.4 (4H, m), 3.93 (3H, s), 6.99 (2H, d, J=8.8Hz), 7.5-7.7 (4H, m), 8.06 (2H, d, J=8.5Hz)

20 MASS (m/z): 491 (M<sup>+</sup>+1)

4'-[4-[Trans-1-methoxy-1,1'-bi(cyclohexyl)-4-yl]-1-

piperazinyl]-1,1'-biphenyl-4-carboxylate

25 NMR (CDCl<sub>3</sub>, δ): 0.8-2.3 (20H, m), 2.6-2.75 (4H, m), 3.15 (3H, s), 3.2-3.4 (4H, m), 3.93 (3H, s), 7.00 (2H, d, J=8.8Hz), 7.5-7.7 (4H, m), 8.06 (2H, d, J=8.4Hz)

MASS (m/z): 491 (M<sup>+</sup>+1)

The following compounds [Preparation 75 to 81] were

30 obtained according to a similar manner to that of Preparation 74.

#### Preparation 75

Benzyl 4-(trans-4-cyclohexylcyclohexyl)-1-

35 piperazinecarboxylate

IR (KBr): 1682, 1466, 1429, 1240  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.75-1.35 (12H, m), 1.5-1.95 (6H, m),  
2.1-2.3 (1H, m), 2.4-2.6 (4H, m), 3.50 (4H, t,  $J=5.0\text{Hz}$ ),  
5.13 (2H, s), 7.25-7.4 (5H, m)

5 ESI MASS (m/z) (Positive): 385 ( $M^+ + 1$ )

#### Preparation 76

Benzyl 4-(trans-4-tert-butylcyclohexyl)-1-piperazinecarboxylate

10 IR (KBr): 1684, 1468, 1525, 1242  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.83 (9H, s), 0.9-1.58 (5H, m), 1.7-2.35 (5H, m),  
2.45-2.6 (4H, m), 3.51 (4H, t,  $J=5.1\text{Hz}$ ), 5.13 (2H, s),  
7.35 (5H, s)

MASS (m/z): 359 ( $M^+ + 1$ )

15

#### Preparation 77

Methyl 4'-[4-(trans-4-ethylcyclohexyl)-1-piperazinyl]-1,1'-biphenyl-4-carboxylate

20 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.8-2.05 (14H, m), 2.2-2.4 (1H, m), 2.65-2.8 (4H, m),  
3.2-3.35 (4H, m), 3.92 (3H, s), 6.99 (2H, d,  $J=8.8\text{Hz}$ ),  
7.55 (2H, d,  $J=8.8\text{Hz}$ ), 7.62 (2H, d,  $J=8.4\text{Hz}$ ),  
8.06 (2H, d,  $J=8.4\text{Hz}$ )

MASS (m/z): 407 ( $M^+ + 1$ )

25 Methyl 4'-[4-(cis-4-ethylcyclohexyl)-1-piperazinyl]-1,1'-biphenyl-4-carboxylate

30 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.88 (3H, t,  $J=7.2\text{Hz}$ ), 1.2-1.7 (11H, m),  
2.2-2.4 (1H, m), 2.65-2.8 (4H, m), 3.2-3.35 (4H, m),  
3.93 (3H, s), 7.00 (2H, d,  $J=8.8\text{Hz}$ ), 7.56 (2H, d,  $J=8.8\text{Hz}$ ),  
7.62 (2H, d,  $J=8.4\text{Hz}$ ), 8.06 (2H, d,  $J=8.4\text{Hz}$ )

MASS (m/z): 407 ( $M^+ + 1$ )

#### Preparation 78

35 Methyl 4'-[4-{trans-4-(trans-4'-methoxycyclohexyl-1'-yl)cyclohexyl-1-yl}-1-piperazinyl]-1,1'-biphenyl-4-

## carboxylate

NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.8-1.4 (10H, m), 1.65-2.4 (9H, m), 2.65-2.8 (4H, m), 2.95-3.15 (1H, m), 3.2-3.35 (4H, m), 3.35 (3H, s), 3.93 (3H, s), 6.99 (2H, d, J=8.8Hz), 7.55 (2H, d, J=8.8Hz), 7.62 (2H, d, J=8.4Hz), 8.06 (2H, d, J=8.4Hz)

5 MASS (m/z): 491 (M<sup>+</sup>+1)

Methyl 4'-[4-[cis-4-(trans-4'-methoxycyclohexyl-1'-yl)cyclohexyl-1-yl]-1-piperazinyl]-1,1'-biphenyl-4-carboxylate

10

NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.8-2.3 (19H, m), 2.6-2.75 (4H, m), 2.95-3.2 (1H, m), 3.2-3.35 (4H, m), 3.35 (3H, s), 3.93 (3H, s), 7.00 (2H, d, J=8.8Hz), 7.56 (2H, d, J=8.8Hz), 7.62 (2H, d, J=8.4Hz), 8.06 (2H, d, J=8.4Hz)

15 MASS (m/z): 491 (M<sup>+</sup>+1)

Preparation 79

Methyl 4'-[4-[4-(trans-4-methoxyphenyl)cyclohexyl]-1-piperazinyl]-1,1'-biphenyl-4-carboxylate

20 NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.4-1.7 (4H, m), 1.9-2.15 (4H, m), 2.3-2.6 (2H, m), 2.75-2.85 (4H, m), 3.2-3.4 (4H, m), 3.79 (3H, s), 3.93 (3H, s), 6.84 (2H, d, J=8.6Hz), 7.01 (2H, d, J=8.8Hz), 7.14 (2H, d, J=8.6Hz), 7.56 (2H, d, J=8.8Hz), 7.63 (2H, d, J=8.4Hz), 7.06 (2H, d, J=8.4Hz)

25 MASS (m/z): 485 (M<sup>+</sup>+1)

Methyl 4'-[4-[4-(cis-4-methoxyphenyl)cyclohexyl]-1-piperazinyl]-1,1'-biphenyl-4-carboxylate

30 NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.5-2.6 (10H, m), 2.6-2.75 (4H, m), 3.2-3.4 (4H, m), 3.79 (3H, s), 3.93 (3H, s), 6.8-6.9 (2H, m), 7.01 (2H, d, J=8.8Hz), 7.19 (2H, d, J=8.6Hz), 7.5-7.65 (4H, m), 8.06 (2H, d, J=8.5Hz)

MASS (m/z): 485 (M<sup>+</sup>+1)

35 Preparation 80

Methyl 4'-[4-[cis-4-methoxy-(4-cyclopentyl)cyclohexyl-1-yl]-1-piperazinyl]-1,1'-biphenyl-4-carboxylate

NMR (CDCl<sub>3</sub>, δ): 1.2-1.9 (16H, m), 2.05-2.4 (2H, m), 2.7-2.85 (4H, m), 3.16 (3H, s), 3.25-3.35 (4H, m), 3.93 (3H, s), 7.00 (2H, d, J=8.8Hz), 7.5-7.7 (4H, m), 8.0-8.1 (2H, m)

MASS (m/z): 477 (M<sup>+</sup>+1)

Methyl 4'-[4-[trans-4-methoxy-(4-cyclopentyl)-cyclohexyl-1-yl]-1-piperazinyl]-1,1'-biphenyl-4-carboxylate

NMR (CDCl<sub>3</sub>, δ): 1.35-1.9 (16H, m), 2.2-2.35 (2H, m), 2.6-3.75 (4H, m), 3.19 (3H, s), 3.2-3.35 (4H, m), 3.93 (3H, s), 7.00 (2H, d, J=8.9Hz), 7.56 (2H, d, J=8.9Hz), 7.62 (2H, d, J=8.6Hz), 8.06 (2H, d, J=8.6Hz)

MASS (m/z): 477 (M<sup>+</sup>+1)

#### Preparation 81

Methyl 4'-[4-(cis-4-methoxy-4-phenylcyclohexyl)-1-piperazinyl]-1,1'-biphenyl-4-carboxylate

NMR (CDCl<sub>3</sub>, δ): 1.5-2.0 (6H, m), 2.1-2.6 (3H, m), 2.75-2.9 (4H, m), 2.99 (3H, s), 3.25-3.4 (4H, m), 3.93 (3H, s), 7.01 (2H, d, J=8.8Hz), 7.2-7.5 (5H, m), 7.57 (2H, d, J=8.8Hz), 7.63 (2H, d, J=8.5Hz), 8.06 (2H, d, J=8.5Hz)

MASS (m/z): 485 (M<sup>+</sup>+1)

#### Preparation 82

A mixture of methyl 4'-[4-[1-methoxy-1,1'-bi(cyclohexyl)-4-yl]-1-piperazinyl]-1,1'-biphenyl-4-carboxylate (440 mg) and 10% sodium hydroxide solution (1.4 ml) in a mixed solvent of methanol (8 ml) and tetrahydrofuran (24 ml) was refluxed for 4 hours. After cooling to ambient temperature, the reaction mixture was poured into cold water and the mixture was adjusted to pH 7 with 1.0 mol/l hydrochloric acid. The resulting precipitates were filtered, washed with water, isopropyl alcohol and diisopropyl ether, then dried to give

4'-[4-[cis-1-methoxy-1,1'-bi(cyclohexyl)-4-yl]-1-piperazinyl]-1,1'-biphenyl-4-carboxylic acid (371 mg).

MASS (m/z): 477 ( $M^+ + 1$ )

- 5        The following compounds [Preparations 83 to 111] were obtained according to a similar manner to that of Preparation 82.

Preparation 83

- 10        4-[5-[4-[4-(Cyclohexylmethyl)-1-piperazinyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid  
NMR (DMSO- $d_6$ ,  $\delta$ ): 0.8-1.8 (11H, m), 2.5-3.5 (10H, m),  
7.1-7.2 (2H, m), 7.92 (2H, d,  $J=8.2$ Hz), 8.12 (4H, s)  
API-ES MASS (m/z): 463.4 ( $M^+ + 1$ )

15

Preparation 84

- 4-[5-[4-[4-(7-Methoxyheptyloxy)cyclohexyl]-1-piperazinyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid  
NMR (DMSO- $d_6$ ,  $\delta$ ): 1.00-2.2 (19H, m), 2.8-3.6 (13H), 3.20 (3H, s), 7.14-7.18 (2H, m), 7.90-7.93 (2H, m), 8.03-8.22 (4H, m)  
ESI MASS (m/z) (Positive): 593.4 ( $M^+ + 1$ )

20

Preparation 85

- 25        4-[5-[4-[4-(8-Methoxyoctyl)cyclohexyl]-1-piperazinyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid  
NMR (DMSO- $d_6$ ,  $\delta$ ): 1.1-2.2 (21H, m), 3.0-3.6 (13H, m), 3.20 (3H, s), 7.14-7.18 (2H, m), 7.78-8.21 (6H, m)  
ESI MASS (m/z) (Negative): 607 ( $M^+ + 1$ )

30

Preparation 86

- 4-[5-[4-[4-(5-Methoxypentyloxy)-1-piperidyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid hydrochloride  
NMR (DMSO- $d_6$ ,  $\delta$ ): 1.25-1.60 (8H, m), 1.80-1.95 (2H, m),  
3.00-3.20 (2H, m), 3.21 (3H, s), 3.25-3.55 (5H, m),

35

3.60-3.80 (2H, m), 7.08 (2H, d,  $J=8.96\text{Hz}$ ), 7.84 (2H, d,  $J=8.48\text{Hz}$ ), 8.10 (4H, s)

ESI MASS (m/z) (Negative): 480.2 ( $M^+ + 1$ )

5 Preparation 87

4-[5-[4-[4-(6-Methoxyhexyloxy)-1-piperidyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.2-1.6 (10H, m), 1.8-2.0 (2H, m), 3.0-3.8 (12H, m), 7.08 (2H, d,  $J=9.0\text{Hz}$ ), 7.84 (2H, d,  $J=8.8\text{Hz}$ ), 8.11 (4H, br s)

(+) APCI MASS (m/z) (Positive): 496.27 ( $M^+ + 1$ )

Preparation 88

4-[5-[4-[4-(4-Methoxybutoxymethyl)-1-piperidyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.2-1.9 (9H, m), 2.8-3.0 (2H, m), 3.2-3.5 (9H, m), 3.8-4.0 (2H, m), 7.07 (2H, d,  $J=8.9\text{Hz}$ ), 7.84 (2H, d,  $J=8.7\text{Hz}$ ), 8.10 (4H, br s)

(+) APCI MASS (m/z) (Positive): 482.20 ( $M^+ + 1$ )

Preparation 89

4-[5-[4-[4-(5-Methoxypentyloxymethyl)-1-piperidyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.1-1.8 (11H, m), 2.7-2.9 (2H, m), 3.2-3.5 (9H, m), 3.8-4.0 (2H, m), 7.07 (2H, d,  $J=9.0\text{Hz}$ ), 7.84 (2H, d,  $J=8.8\text{Hz}$ ), 8.0-8.2 (4H, m)

ESI MASS (m/z) (Negative): 494.3 ( $M^+ + 1$ )

Preparation 90

4-[5-[6-[Cis-4-(4-methylcyclohexyl)-1-piperazinyl]-3-pyridyl]-1,3,4-thiadiazol-2-yl]benzoic acid

(+) APCI MASS (m/z) (Positive): 464.13 ( $M^+ + 1$ )

Preparation 91

4-[5-[6-[Trans-4-(4-methylcyclohexyl)-1-piperazinyl]-3-



pyridyl]-1,3,4-thiadiazol-2-yl]benzoic acid  
(+) APCI MASS (m/z) (Positive): 464.20 ( $M^+ + 1$ )

Preparation 92

- 5      4-[5-[6-[Cis-4-(4-ethylcyclohexyl)-1-piperazinyl]-3-pyridyl]-1,3,4-thiadiazol-2-yl]benzoic acid  
ESI MASS (m/z) (Positive): 478.3 ( $M^+ + 1$ )

Preparation 93

- 10     4-[5-[6-[Trans-4-(4-ethylcyclohexyl)-1-piperazinyl]-3-pyridyl]-1,3,4-thiadiazol-2-yl]benzoic acid  
(+) APCI MASS (m/z) (Positive): 478.3 ( $M^+ + 1$ )

Preparation 94

- 15     4-[2-[4-(1-Cyclohexyl-4-piperidyl)phenyl]imidazo[2,1-b]-  
[1,3,4]thiadiazol-6-yl]benzoic acid hydrochloride  
IR (KBr): 2937, 1699, 1608, 1471, 1414, 1373, 1255,  
1174  $\text{cm}^{-1}$   
20     NMR (DMSO- $d_6$ ,  $\delta$ ): 1.0-2.1 (14H, m), 2.8-4.0 (6H, m), 7.4-  
8.0 (8H, m), 8.86 (1H, s)  
(+) APCI MASS (m/z): 487.33 ( $M^+ + 1$ )

Preparation 95

- 25     4-[2-[4-[Cis-4-(4-methylcyclohexyl)-1-piperazinyl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid hydrochloride  
ESI MASS (m/z) (Positive): 502.3 ( $M^+ + 1$ )

Preparation 96

- 30     4'-[4-(Trans-4-cyclohexylcyclohexyl)-1-piperazinyl]-  
1,1'-biphenyl-4-carboxylic acid  
ESI MASS (m/z): 447 ( $M^+ + 1$ )

35     Preparation 97

4'-[4-(Trans-4-tert-butylcyclohexyl)-1-piperazinyl]-  
1,1'-biphenyl-4-carboxylic acid  
ESI MASS (m/z): 421 ( $M^+$ +1)

5 Preparation 98

4'-[4-(Trans-4-ethylcyclohexyl)-1-piperazinyl]-1,1'-  
biphenyl-4-carboxylic acid  
IR (KBr): 1699, 1602, 1525, 1377  $\text{cm}^{-1}$   
MASS (m/z): 393 ( $M^+$ +1)

10

Preparation 99

4'-[4-(Cis-4-ethylcyclohexyl)-1-piperazinyl]-1,1'-  
biphenyl-4-carboxylic acid  
IR (KBr): 1691, 1603, 1529, 1452, 1381  $\text{cm}^{-1}$   
MASS (m/z): 393 ( $M^+$ +1)

15

Preparation 100

4'-[4-[Trans-1-methoxy-1,1'-bi(cyclohexyl)-4-yl]-1-  
piperazinyl]-1,1'-biphenyl-4-carboxylic acid  
MASS (m/z): 477 ( $M^+$ +1)

20

Preparation 101

4'-[4-(Cis-4-(trans-4-methoxycyclohexyl-1-yl)-  
cyclohexyl-1-yl)-1-piperazinyl]-1,1'-biphenyl-4-carboxylic  
acid  
MASS (m/z): 477 ( $M^+$ +1)

25

Preparation 102

4'-[4-[Trans-4-(cis-4-methoxycyclohexyl-1-  
yl)cyclohexyl-1-yl]-1-piperazinyl]-1,1'-biphenyl-4-  
carboxylic acid  
MASS (m/z): 477 ( $M^+$ +1)

30

Preparation 103

4'-[4-[Cis-4-(4-methoxyphenyl)cyclohexyl]-1-

35

piperazinyll-1,1'-biphenyl-4-carboxylic acid

MASS (m/z): 471 ( $M^+$ +1)

Preparation 104

- 5        4'-[4-(4-Methoxyphenyl)-1-piperazinyll-1,1'-biphenyl-4-carboxylic acid

MASS (m/z): 491 ( $M^+$ +1)

Preparation 105

- 10      4'-[4-[Trans-4-(4-methoxyphenyl)cyclohexyl]-1-piperazinyll-1,1'-biphenyl-4-carboxylic acid

MASS (m/z): 471 ( $M^+$ +1)

Preparation 106

- 15      4'-[4-(4,4-Dimethylcyclohexyl)-1-piperazinyll-1,1'-biphenyl-4-carboxylic acid

MASS (m/z): 393 ( $M^+$ +1)

Preparation 107

- 20      4'-[4-[Cis-4-methoxy-(4-cyclopentyl)cyclohexyl-1-yl]-1-piperazinyll-1,1'-biphenyl-4-carboxylic acid

MASS (m/z): 463 ( $M^+$ +1)

Preparation 108

- 25      4'-[4-[Trans-4-methoxy-(4-cyclopentyl)cyclohexyl-1-yl]-1-piperazinyll-1,1'-biphenyl-4-carboxylic acid

MASS (m/z): 461 ( $M^+$ +1)

Preparation 109

- 30      4'-[4-(Cis-4-methoxy-4-phenylcyclohexyl)-1-piperazinyll-1,1'-biphenyl-4-carboxylic acid

MASS (m/z): 471 ( $M^+$ +1)

Preparation 110

- 35      4'-[5-[4-[4-(4-Methylenecyclohexyl)-1-piperazinyll]-

phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid dihydrochloride

IR (KBr): 3400, 2939, 2852, 2592, 2455, 1705, 1603,  
1522  $\text{cm}^{-1}$

5 NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 1.20-1.80 (4H, m), 1.80-2.40 (4H, m),  
2.50-2.60 (4H, m), 3.10-3.30 (4H, m), 4.70 (1H, br s),  
7.16 (2H, d,  $J=8.6\text{Hz}$ ), 7.92 (2H, d,  $J=9.2\text{Hz}$ ),  
8.00-8.30 (4H, m)

API-ES MASS ( $m/z$ ) (Positive): 463 ( $M^+-2\text{HCl}+1$ )

10 Preparation 111

4-[5-[4-[4-(4-Phenylcyclohexyl)-1-piperazinyl]-  
phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid

API-ES MASS ( $m/z$ ): 525.3 ( $M^++1$ )

15 Preparation 112

A mixture of 4'-[cis-4-[1-methoxy-1,1'-bi(cyclohexyl)-  
4-yl]-1-piperazinyl]-1,1'-biphenyl-4-carboxylic acid (367 mg),  
1-hydroxybenzotriazole (208 mg), 1-ethyl-3-(3'-  
dimethylaminopropyl)carbodiimide hydrochloride (443 mg) and  
20 triethylamine (0.216 ml) in methylene chloride (37 ml) was  
stirred for 23.5 hours at room temperature then evaporated under  
reduced pressure. Water was added to the residue and the  
resulting precipitate collected by filtration, washed with water,  
isopropyl alcohol and diisopropyl ether, then dried to give  
25 1-[[4'-[cis-4-[1-methoxy-1,1'-bi(cyclohexyl)-4-yl]-1-  
piperazinyl]-1,1'-biphenyl-4-yl]carbonyloxy]-1H-1,2,3-  
benzotriazole (399 mg).

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.8-2.2 (19H, m), 2.3-2.5 (1H, m), 2.75-  
2.95 (4H, m), 3.11 (3H, s), 3.25-3.5 (4H, m), 7.03 (2H,  
30 d,  $J=8.8\text{Hz}$ ), 7.4-7.7 (5H, m), 7.79 (2H, d,  $J=8.5\text{Hz}$ ),  
8.12 (1H, d,  $J=8.1\text{Hz}$ ), 8.30 (2H, d,  $J=8.5\text{Hz}$ )

MASS ( $m/z$ ): 594 ( $M^++1$ )

The following compounds [Preparations 113 to 138] were  
35 obtained according to a similar manner to that of Preparation

112.

Preparation 113

1-[4-[5-[4-[4-(Cyclohexylmethyl)-1-piperazinyl]phenyl]-  
5 1,3,4-thiadiazol-2-yl]benzoyloxy]-1H-1,2,3-benzotriazole  
IR (KBr): 2922, 2845, 1780, 1603, 1441, 1416, 1232, 984,  
822.  $\text{cm}^{-1}$   
NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.8-1.9 (11H, m), 2.22 (2H, d,  $J=7.1\text{Hz}$ ),  
2.5-2.7 (4H, m), 3.3-3.5 (4H, m), 6.9-8.5 (12H, m)  
10 (+) APCI MASS ( $m/z$ ): 580.13 ( $M^++1$ )

Preparation 114

1-[4-[5-[4-[4-(7-Methoxyheptyloxy)cyclohexyl]-1-  
piperazinyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoyloxy]-1H-  
15 1,2,3-benzotriazole  
IR (KBr): 2931, 2856, 1778, 1603, 1441, 1416, 1234, 1093,  
984  $\text{cm}^{-1}$   
NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.0-2.2 (19H, m), 2.4-3.7 (13H, m), 3.33 (3H,  
s), 6.8-8.5 (12H, m)  
20

Preparation 115

1-[4-[5-[4-[4-(8-Methoxyoctyloxy)cyclohexyl]-1-  
piperazinyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoyloxy]-1H-  
1,2,3-benzotriazole  
25 IR (KBr): 2931, 2856, 1778, 1605, 1441, 1416, 1234, 1093,  
984  $\text{cm}^{-1}$   
NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.0-2.2 (21H, m), 2.7-3.7 (13H, m), 3.33 (3H,  
s), 6.9-8.5 (12H, m)

Preparation 116

1-[4-[5-[4-[4-(5-Methoxypentyloxy)-1-piperidyl]phenyl]-  
1,3,4-thiadiazol-2-yl]benzoyloxy]-1H-1,2,3-benzotriazole  
NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 1.30-1.80 (8H, m), 1.85-2.10 (2H, m),  
3.00-3.25 (2H, m), 3.34 (3H, s), 3.35-3.55 (5H, m),  
35 3.60-3.80 (2H, m), 6.97 (2H, d,  $J=8.95\text{Hz}$ ), 7.35-7.65

(3H, m), 7.90 (2H, d, J=8.81Hz), 8.13 (2H, d, J=8.19Hz),  
8.23 (2H, d, J=8.46Hz), 8.39 (2H, d, J=8.41Hz)

Preparation 117

- 5 1-[4-[5-[4-[4-(6-Methoxyhexyloxy)-1-piperidyl]phenyl]-  
1,3,4-thiadiazol-2-yl]benzoyloxy]-1H-1,2,3-benzotriazole  
IR (KBr): 2931, 2856, 1778, 1603, 1439, 1416, 1230, 1109,  
982  $\text{cm}^{-1}$   
NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.3-2.1 (12H, m), 3.0-3.3 (2H, m), 3.33 (3H,  
10 s), 3.3-3.6 (5H, m), 3.6-3.8 (2H, m), 6.97 (2H, d,  
J=8.9Hz), 7.4-7.7 (3H, m), 7.90 (2H, d, J=8.8Hz),  
8.1-8.3 (3H, m), 8.3-8.5 (2H, m)  
(+) APCI MASS (m/z) (Positive): 612.93 ( $\text{M}^+ + 1$ )

15 Preparation 118

- 1-[4-[5-[4-[4-(4-Methoxybutoxymethyl)-1-  
piperidyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoyloxy]-1H-  
1,2,3-benzotriazole  
IR (KBr): 1778, 1603, 1439, 1412, 1248, 1230, 1115, 1090,  
20 984  $\text{cm}^{-1}$   
NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 1.0-2.1 (9H, m), 2.8-3.0 (2H, m), 3.1-  
3.5 (6H, m), 3.34 (3H, s), 3.8-4.0 (2H, m), 6.96 (2H,  
d, J=9.0Hz), 7.3-7.6 (3H, m), 7.90 (2H, d, J=8.9Hz),  
8.12 (1H, d, J=7.2Hz), 8.2-8.3 (2H, m), 8.3-8.5 (2H,  
25 m)

Preparation 119

- 1-[4-[5-[4-[4-(5-Methoxypentyloxymethyl)-1-  
piperidyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoyloxy]-1H-  
30 1,2,3-benzotriazole  
NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.1-2.0 (11H, m), 2.7-2.9 (2H, m), 3.2-3.5  
(6H, m), 3.33 (3H, s), 3.7-3.9 (2H, m), 6.90 (2H, m,  
J=9.0Hz), 7.3-7.6 (3H, m), 7.83 (2H, d, J=8.8Hz), 8.06  
(1H, d, J=8.2Hz), 8.16 (2H, d, J=8.5Hz), 8.33 (2H, d,  
35 J=8.5Hz)

(+) APCI MASS (m/z) (Positive): 613.13 ( $M^+ + 1$ )

Preparation 120

1-[4-[5-[6-[4-(4-Methylcyclohexyl)-1-piperazinyl]-3-pyridyl]-1,3,4-thiadiazol-2-yl]benzoyloxy]-1H-1,2,3-benzotriazole

IR (KBr): 2947, 2922, 1778, 1601, 1429, 1400, 1236, 987  $\text{cm}^{-1}$   
NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.8-1.5 (8H, m), 1.7-1.9 (2H, m), 1.9-2.1 (2H, m), 2.6-3.0 (1H, m), 3.0-3.2 (4H, br s), 3.5-4.2 (4H, br s), 6.6-6.8 (1H, m), 7.4-8.5 (9H, m), 8.75 (1H, d,  $J=2.3\text{Hz}$ )

ESI MASS (m/z) (Positive): 581.3 ( $M^+ + 1$ )

Preparation 121

1-[4-[5-[6-[4-(4-Ethylcyclohexyl)-1-piperazinyl]-3-pyridyl]-1,3,4-thiadiazol-2-yl]benzoyloxy]-1H-1,2,3-benzotriazole

IR (KBr): 2926, 1780, 1703, 1601, 1508, 1429, 1402, 1379, 1242, 984  $\text{cm}^{-1}$   
NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.8-1.0 (5H, m), 1.2-1.9 (8H, m), 1.9-2.5 (2H, m), 2.6-2.8 (4H, m), 3.6-3.8 (4H, m), 6.73 (1H, d,  $J=9.1\text{Hz}$ ), 7.4-7.7 (3H, m), 8.0-8.5 (6H, m), 8.74 (1H, d,  $J=2.3\text{Hz}$ )

ESI MASS (m/z) (Positive): 595.3 ( $M^+ + 1$ )

Preparation 122

1-[4-[5-[6-[Trans-4-(4-ethylcyclohexyl)-1-piperazinyl]-3-pyridyl]-1,3,4-thiadiazol-2-yl]benzoyloxy]-1H-1,2,3-benzotriazole

IR (KBr): 2924, 2850, 1778, 1601, 1429, 1402, 1362, 1244, 984  $\text{cm}^{-1}$   
NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.8-1.5 (10H, m), 1.7-2.1 (4H, m), 2.3-2.6 (1H, m), 2.7-2.9 (4H, br s), 3.6-3.9 (4H, br s), 6.6-6.8 (1H, m), 7.4-7.7 (3H, m), 7.9-8.5 (6H, m), 8.74 (1H, d,  $J=2.3\text{Hz}$ )

ESI MASS (m/z) (Positive): 595.3 ( $M^+ + 1$ )

Preparation 123

1-[4-[2-[4-[Cis-4-(4-methylcyclohexyl)-1-piperazinyl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoyloxy]-1H-1,2,3-benzotriazole

IR (KBr): 1795, 1697, 1649, 1605, 1539, 1473, 1383, 1234, 1095, 1018  $\text{cm}^{-1}$

10 Preparation 124

1-[4'-[4-(Trans-4-cyclohexylcyclohexyl)-1-piperazinyl]-1,1'-biphenyl-4-yl]carbonyloxy-1H-1,2,3-benzotriazole

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.8-2.5 (21H, m), 2.8-3.0 (4H, m), 3.3-3.45 (4H, m), 7.03 (2H, d,  $J=8.7\text{Hz}$ ), 7.4-7.7 (5H, m), 7.79 (2H, d,  $J=8.4\text{Hz}$ ), 8.12 (1H, d,  $J=8.4\text{Hz}$ ), 8.30 (2H, d,  $J=8.3\text{Hz}$ )

MASS (m/z): 447 ( $M^+ + 1$ )

Preparation 125

20 1-[4-[5-[4-[4-(4-Methylenecyclohexyl)-1-piperazinyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoyloxy]-1H-1,2,3-benzotriazole

IR (KBr): 3425, 3404, 2929, 2831, 1780, 1600  $\text{cm}^{-1}$

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 1.10-1.50 (4H, m), 1.60-2.20 (4H, m), 2.20-2.40 (3H, m), 2.50-2.80 (4H, m), 4.62 (1H, br s), 7.17 (2H, d,  $J=9.1\text{Hz}$ ), 7.70-7.60 (2H, m), 7.65 (1H, d,  $J=8.0\text{Hz}$ ), 7.75-8.00 (3H, m), 8.10-8.30 (4H, m)

API-ES MASS (m/z) (Positive): 584

30 Preparation 126

1-[4'-[4-(Trans-4-tert-butylcyclohexyl)-1-piperazinyl]-1,1'-biphenyl-4-yl]carbonyloxy-1H-1,2,3-benzotriazole

IR (KBr): 1770, 1570, 1236  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.86 (9H, s), 0.9-1.4 (5H, m), 1.7-2.5 (5H, m), 2.7-2.85 (4H, m), 3.2-3.4 (4H, m), 6.9-7.1 (2H, m)



m), 7.3-7.7 (5H, m), 7.79 (2H, d,  $J=8.5\text{Hz}$ ), 8.11 (1H, d,  $J=8.4\text{Hz}$ ), 8.30 (2H, d,  $J=8.4\text{Hz}$ )

MASS (m/z): 538 ( $M^+ + 1$ )

#### 5 Preparation 127

1-[4'-[4-(Trans-4-ethylcyclohexyl)-1-piperazinyl]-1,1'-biphenyl-4-yl]carbonyloxy-1H-1,2,3-benzotriazole

#### Preparation 128

10 1-[4'-[4-(Cis-4-ethylcyclohexyl)-1-piperazinyl]-1,1'-biphenyl-4-yl]carbonyloxy-1H-1,2,3-benzotriazole

#### Preparation 129

15 1-[4'-[4-[Trans-1-methoxy-1,1'-bi(cyclohexyl)-4-yl]-1-piperazinyl]-1,1'-biphenyl-4-yl]carbonyloxy-1H-1,2,3-benzotriazole

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.8-2.6 (20H, m), 2.7-3.0 (4H, m), 3.15 (3H, s), 3.3-3.6 (4H, m), 7.03 (2H, d,  $J=8.7\text{Hz}$ ), 7.3-7.7 (5H, m), 7.79 (2H, d,  $J=8.4\text{Hz}$ ), 8.12 (1H, d,  $J=8.1\text{Hz}$ ), 8.31 (2H, d,  $J=8.4\text{Hz}$ )

20 MASS (m/z): 594 ( $M^+ + 1$ )

#### Preparation 130

25 1-[4'-[4-[Cis-4-(cis-4'-methoxycyclohexyl)-1'-yl)cyclohexyl-1-yl]-1-piperazinyl]-1,1'-biphenyl-4-yl]carbonyloxy-1H-1,2,3-benzotriazole

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.7-2.6 (19H, m), 2.7-3.2 (5H, m), 3.35 (3H, s), 3.3-3.5 (4H, m), 7.03 (2H, d,  $J=8.8\text{Hz}$ ), 7.35-7.7 (5H, m), 7.79 (2H, d,  $J=8.5\text{Hz}$ ), 8.12 (1H, d,  $J=8.2\text{Hz}$ ), 8.30 (2H, d,  $J=8.5\text{Hz}$ )

30 MASS (m/z): 594 ( $M^+ + 1$ )

#### Preparation 131

35 1-[4'-[4-[Trans-4-(cis-4'-methoxycyclohexyl)-1'-yl)cyclohexyl-1-yl]-1-piperazinyl]-1,1'-biphenyl-4-

yl]carbonyloxy-1H-1,2,3-benzotriazole

NMR (CDCl<sub>3</sub>, δ): 0.8-1.5 (10H, m), 1.6-2.6 (9H, m), 2.8-3.2 (5H, m), 3.35 (3H, s), 3.3-3.5 (4H, m), 7.03 (2H, d, J=8.8Hz), 7.4-7.7 (5H, m), 7.78 (2H, d, J=8.5Hz), 8.12 (1H, d, J=8.2Hz), 8.30 (2H, d, J=8.5Hz)

MASS (m/z): 594 (M<sup>+</sup>+1)

#### Preparation 132

1-[4'-[4-[Cis-4-(4-methoxyphenyl)cyclohexyl]-1-piperazinyl]-1,1'-biphenyl-4-yl]carbonyloxy-1H-1,2,3-benzotriazole

NMR (CDCl<sub>3</sub>, δ): 1.5-2.9 (14H, m), 3.3-3.5 (4H, m), 3.79 (3H, s), 6.85 (2H, d, J=8.7Hz), 7.03 (2H, d, J=8.8Hz), 7.21 (2H, d, J=8.7Hz), 7.4-7.7 (5H, m), 7.79 (2H, d, J=8.5Hz), 8.12 (1H, d, J=8.2Hz), 8.30 (2H, d, J=8.5Hz)

MASS (m/z): 588 (M<sup>+</sup>+1)

#### Preparation 133

1-[4'-[4-(4-Methoxyphenyl)-1-piperazinyl]-1,1'-biphenyl-4-yl]carbonyloxy-1H-1,2,3-benzotriazole

NMR (CDCl<sub>3</sub>, δ): 3.2-3.55 (8H, m), 3.79 (3H, s), 6.8-7.2 (6H, m), 7.4-7.9 (7H, m), 8.0-8.15 (2H, m), 8.31 (1H, d, J=8.2Hz)

MASS (m/z): 506 (M<sup>+</sup>+1)

#### Preparation 134

1-[4'-[4-[4-(Trans-4-methoxyphenyl)cyclohexyl]-1-piperazinyl]-1,1'-biphenyl-4-yl]carbonyloxy-1H-1,2,3-benzotriazole

NMR (CDCl<sub>3</sub>, δ): 1.4-2.35 (8H, m), 2.3-2.5 (2H, m), 2.8-3.0 (4H, m), 3.3-3.5 (4H, m), 3.79 (3H, s), 6.85 (2H, d, J=8.7Hz), 7.04 (2H, d, J=8.8Hz), 7.13 (2H, d, J=8.7Hz), 7.4-7.7 (5H, m), 7.79 (2H, d, J=8.5Hz), 8.12 (1H, d, J=8.2Hz), 8.30 (2H, d, J=8.5Hz)

MASS (m/z): 588 (M<sup>+</sup>+1)

Preparation 135

1-[4'-[4-(4,4-Dimethylcyclohexyl)-1-piperazinyl]-1,1'-biphenyl-4-yl]carbonyloxy-1H-1,2,3-benzotriazole

5 NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.92 (6H, s), 1.1-1.9 (8H, m), 2.2-2.5 (1H, m), 2.75-2.95 (4H, m), 3.3-3.45 (4H, m), 7.03 (2H, d, J=8.8Hz), 7.4-7.7 (5H, m), 7.79 (2H, d, J=8.5Hz), 8.12 (1H, d, J=8.2Hz), 8.30 (2H, d, J=8.5Hz)

MASS (m/z): 510 (M<sup>+</sup>+1)

10

Preparation 136

1-[4'-[4-[Cis-4-methoxy-(4-cyclopentyl)cyclohexyl-1-yl]-1-piperazinyl]-1,1'-biphenyl-4-yl]carbonyloxy-1H-1,2,3-benzotriazole

15 IR (KBr): 1776, 1597 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.2-2.0 (16H, m), 2.1-2.45 (2H, m), 2.75-2.9 (4H, m), 3.16 (3H, s), 3.25-3.4 (4H, m), 7.03 (2H, d, J=8.9Hz), 7.4-7.7 (5H, m), 7.79 (2H, d, J=8.6Hz), 8.11 (1H, d, J=8.2Hz), 8.30 (2H, d, J=8.6Hz)

20 MASS (m/z): 579 (M<sup>+</sup>)

Preparation 137

1-[4'-4-[Trans-4-methoxy-(4-cyclopentyl)cyclohexyl-1-yl]-1-piperazinyl]carbonyloxy-1H-1,2,3-benzotriazole

25 IR (KBr): 1772, 1597 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.35-2.4 (18H, m), 2.65-2.8 (4H, m), 3.20 (3H, s), 3.25-3.4 (4H, m), 7.03 (2H, d, J=8.9Hz), 7.4-7.7 (5H, m), 7.79 (2H, d, J=8.6Hz), 8.05-8.15 (1H, m), 8.25-8.35 (2H, m)

30 MASS (m/z): 580 (M<sup>+</sup>+1)

Preparation 138

1-[4'-[4-(Cis-4-methoxy-4-phenylcyclohexyl)-1-piperazinyl]-1,1'-biphenyl-4-yl]carbonyloxy-1H-1,2,3-benzotriazole

35

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.5-2.6 (9H, m), 2.8-2.95 (4H, m), 2.99 (3H, s), 3.3-3.45 (4H, m), 7.05 (2H, d, J=8.9Hz), 7.2-7.7 (10H, m), 7.79 (2H, d, J=8.6Hz), 8.11 (1H, d, J=8.1Hz), 8.30 (2H, d, J=8.6Hz)

5 MASS (m/z): 588 (M<sup>+</sup>+1)

#### Preparation 139

A mixture of cesium trichloride (24.9 g) in tetrahydrofuran (45 ml) was stirred at room temperature for 5 hours. 1,4-Dioxaspiro[4.5]decan-8-one (1.4 g) was added to the solution and stirred at room temperature for 1 hour. To the solution was added dropwise with stirring phenylmagnesium chloride (3.0M solution in dimethyl ether) (33.7 ml) at 0°C. The reaction mixture was quenched with 10% acetic acid aqueous solution. Dimethyl ether was added to the solution. The organic layer was washed with brine, sodium hydrogen carbonate solution and brine and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (3:1 hexane-ethyl acetate elution) to give 8-phenyl-1,4-dioxaspiro[4.5]decan-8-ol (5.94 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.65-2.3 (8H, m), 3.99 (4H, s), 4.03 (1H, s), 7.2-7.6 (5H, m)

MASS (m/z): 257 (M<sup>+</sup>+23)

25

The following compound was obtained according to a similar manner to that of Preparation 139.

#### Preparation 140

30 8-Cyclopentyl-1,4-dioxaspiro[4.5]decan-8-ol

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.2-2.1 (17H, m), 3.9-4.05 (4H, m), 4.03 (1H, s)

MASS (m/z): 249 (M<sup>+</sup>+23)

35 Preparation 141

To a solution of 8-phenyl-1,4-dioxaspiro[4.5]decan-8-ol (5.76 g) and iodomethane (4.59 ml) in N,N-dimethylformamide (58 ml) was added sodium hydride (60% dispersion in mineral oil) (1.97 g) at 0°C. The solution was stirred for 2 hours at 0°C and at room temperature for 7.5 hours. The reaction mixture was added to a mixture of water and ether. The organic layer was washed with brine and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (5:1 hexane-ethyl acetate elution) to give 8-methoxy-8-phenyl-1,4-dioxaspiro[4.5]decane (5.968 g).

NMR (CDCl<sub>3</sub>, δ): 1.6-2.15 (8H, m), 3.00 (3H, s), 3.9-4.05 (4H, m), 7.2-7.5 (5H, m)

15

The following compounds [Preparations 142 and 143] were obtained according to a similar manner to that of Preparation 141.

#### 20 Preparation 142

4'-Methoxy-1,1'-bi(cyclohexyl)-4-ol

NMR (CDCl<sub>3</sub>, δ): 0.8-2.2 (18H, m), 2.9-3.6 (6H, m)

MASS (m/z): 235 (M<sup>+</sup>+23)

#### 25 Preparation 143

8-Cyclopentyl-8-methoxy-1,4-dioxaspiro[4.5]decane

NMR (CDCl<sub>3</sub>, δ): 1.25-2.35 (17H, m), 3.16 (3H, s), 3.9-4.0 (4H, m)

#### 30 Preparation 144

A solution of 8-methoxy-8-phenyl-1,4-dioxaspiro[4.5]decane (5.96 g) and 3N-hydrochloric acid (24 ml) in tetrahydrofuran was stirred at room temperature for 24 hours. The reaction mixture was added to a mixture of sodium hydrogen carbonate solution and dimethyl ether. The organic layer was

washed with sodium hydrogen carbonate solution and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (1:0-150:1 dichloromethane-methanol elution) to give 4-methoxy-4-phenylcyclohexanone (3.6 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 2.0-2.9 (8H, m), 3.09 (3H, s), 7.25-7.5 (5H, m)

MASS (m/z): 227 (M<sup>+</sup>+23)

10

The following compound was obtained according to a similar manner to that of Preparation 144.

#### Preparation 145

15 4-Cyclopentyl-4-methoxycyclohexanone

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.2-2.4 (15H, m), 2.45-2.7 (2H, m), 3.27 (3H, s)

MASS (m/z): 219 (M<sup>+</sup>+23)

#### 20 Preparation 146

A mixture of 4-[5-[4-[4-(4-phenylcyclohexyl)-1-piperazinyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid (0.81 g), 0-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (0.66 g) and N,N-diisopropylethylamine (0.51 ml) in 1-methyl-2-pyrrolidinone (16 ml) was stirred for 25 2 hours at 50°C. The reaction mixture was poured into water. Then the resulting precipitate was collected by filtration and washed with water to give 1-4-[5-[4-[4-(4-phenylcyclohexyl)-1-piperazinyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoyleoxy-1H-30 1,2,3-benzotriazole (0.97 g).

IR (KBr): 1780, 1603, 1444, 1414, 1234, 1188, 980, 843 cm<sup>-1</sup>  
NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.6-2.2 (8H, m), 2.3-2.5 (1H, m), 2.7-2.9 (5H, m), 3.4-3.6 (4H, m), 6.9-8.5 (17H, m)

(+) APCI MASS (m/z): 642.07 (M<sup>+</sup>+1)

35

The following compounds [Preparations 147 and 148] were obtained according to a similar manner to that of Preparation 146.

5 Preparation 147

1-[4-[5-[6-[4-(4-Methylcyclohexyl)-1-piperazinyl]-3-pyridyl]-1,3,4-thiadiazol-2-yl]benzoyloxy]-1H-1,2,3-benzotriazole

IR (KBr): 2943, 2918, 1782, 1601, 1427, 1402, 987, 845  $\text{cm}^{-1}$

10 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.94 (3H, d,  $J=6.9\text{Hz}$ ), 1.4-1.8 (9H, m),  
2.3-2.5 (1H, m), 2.5-3.9 (4H, m), 3.7-3.9 (4H, m), 6.74  
(1H, d,  $J=9.0\text{Hz}$ ), 7.4-7.7 (3H, m), 8.1-8.5 (6H, m),  
8.74 (1H, d,  $J=2.3\text{Hz}$ )

MASS ( $m/z$ ) (Positive): 581.3 ( $M^++1$ )

15

Preparation 148

1-4-[2-[4-(1-Cyclohexyl-1-piperidyl)phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoyloxy-1H-1,2,3-benzotriazole

IR (KBr): 2926, 1776, 1608, 1471, 1230, 1176, 980, 845  $\text{cm}^{-1}$

20 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.0-2.7 (18H, m), 3.1-3.3 (2H, m), 7.2-8.4  
(13H, m)

(+) APCI MASS ( $m/z$ ): 604.13 ( $M^++1$ )

Preparation 149

25 To a solution of 1,4-dioxaspiro[4.5]decan-8-ol (9.5 g) in N,N-dimethylformamide (200 ml) was added portionwise sodium hydride (abt. 60% oil suspension) (2.6 g) under ice-cooling and nitrogen atmosphere. After stirring for 2 hours at room temperature, the reaction mixture was stirred for 1 hour at 60°C.

30 To the reaction mixture was added a solution of 7-methoxyheptyl 4-methylbenzenesulfonate (15.0 g) in N,N-dimethylformamide (50 ml) at 60°C and then the reaction mixture was stirred for 2 hours at 60°C. After being cooled to room temperature, the reaction mixture was poured into a mixture of ethyl acetate and water.

35 The organic layer was successively washed with water and brine

and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel eluting with a mixture of hexane and ethyl acetate (10:1-5:1). The eluted fractions containing the desired product were collected and evaporated in vacuo to give 8-(7-methoxyheptyloxy)-1,4-dioxaspiro[4.5]decane (9.77 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.3-1.9 (18H, m), 3.33 (3H, s), 3.3-3.5 (5H, m), 3.94 (4H, s)

ESI MASS (m/z) (Positive): 309.3 (M<sup>+</sup>+Na)

The following compounds [Preparations 150 and 151] were obtained according to a similar manner to that of Preparation 149.

#### Preparation 150

8-(8-Methoxyoctyloxy)-1,4-dioxaspiro[4.5]decane

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.2-1.9 (20H, m), 3.33 (3H, s), 3.3-3.5 (5H, m), 3.94 (4H, s)

ESI MASS (m/z) (Positive): 323.3 (M<sup>+</sup>+Na)

#### Preparation 151

tert-Butyl 4-(6-methoxyhexyloxy)-1-piperidinecarboxylate

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.3-1.7 (12H, m), 1.45 (9H, s), 1.7-1.9 (1H, m), 3.0-3.2 (2H, m), 3.33 (3H, s), 3.3-3.5 (4H, m), 3.7-3.9 (2H, m)

(+) APCI MASS (m/z) (Positive): 216.07 (M<sup>+</sup>+1-Boc)

#### Preparation 152

A mixture of ethyl 4-[(4-(7-methoxyheptyloxy)-cyclohexyl-1-piperazinyl]benzoate (2.8 g) and hydrazine monohydrate (26 ml) in ethanol (56 ml) and tetrahydrofuran (22 ml) was stirred for 15 hours at 100°C. After being cooled to room temperature, the reaction mixture was poured into water. The solvent was evaporated in vacuo and the residue was extracted with ethyl acetate. The extract was washed with water and dried



over magnesium sulfate. The solvent was evaporated in vacuo to give 4-[4-4-(7-methoxyheptyloxy)cyclohexyl-1-piperazinyl]benzohydrazide (2.58 g).

IR (Neat): 2933, 2858, 1608, 1512, 1454, 1240, 1113  $\text{cm}^{-1}$

5 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.2-2.2 (18H, m), 2.2-2.4 (1H, m), 2.62 (4H, m), 3.33 (3H, s), 3.2-3.5 (9H, m), 4.06 (2H, br s), 6.8-6.9 (2H, m), 7.30 (1H, s), 7.6-7.7 (2H, m)

(+) APCI MASS (m/z): 447.47 ( $\text{M}^+ + 1$ )

10 The following compounds [Preparations 153 to 164] were obtained according to a similar manner to that of Preparation 152.

#### Preparation 153

15 4-[4-(4-Phenylcyclohexyl)-1-piperazinyl]benzohydrazide

APCI MASS (m/z) (Positive): 379.4 ( $\text{M}^+ + 1$ )

#### Preparation 154

20 4-[4-(4-Methylenecyclohexyl)-1-piperazinyl]benzohydrazine

IR (KBr): 3429, 3402, 3307, 3280, 2933, 2837, 1608, 1504  $\text{cm}^{-1}$

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 1.20-1.50 (2H, m), 1.60-2.20 (4H, m), 2.20-2.30 (2H, m), 2.50-2.70 (4H, m), 3.10-3.30 (4H, m), 4.36 (2H, br s), 4.61 (1H, s), 6.91 (2H, d,  $J=8.9\text{Hz}$ ), 7.69 (2H, d,  $J=8.8\text{Hz}$ ), 9.45 (1H, br s)

25 MASS (m/z): 317 ( $\text{M}^+ + 1$ )

#### Preparation 155

30 4-[4-(Cyclohexylmethyl)-1-piperazinyl]benzohydrazide

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 0.70-1.00 (2H, m), 1.10-1.80 (9H, m), 2.11 (2H, d,  $J=7.2\text{Hz}$ ), 2.41-2.46 (4H, m), 3.19-3.24 (4H, m), 4.36 (2H, s), 6.92 (2H, d,  $J=8.9\text{Hz}$ ), 7.69 (2H, d,  $J=8.9\text{Hz}$ ), 9.46 (1H, s)

APCI MASS (m/z) (Positive): 317 ( $\text{M}^+ + 1$ )

35

Preparation 156

4-[4-[4-(8-Methoxyoctyloxy)cyclohexyl]-1-piperazinyl]benzohydrazide

IR (Neat): 2931, 2856, 1703, 1608, 1512, 1454, 1240,  
1113  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.2-2.2 (20H, m), 2.2-2.4 (1H, m), 2.6-2.8 (4H, m), 3.1-3.5 (9H, m), 3.33 (3H, s), 4.05 (2H, br s), 6.8-6.9 (2H, m), 7.27 (1H, s), 7.6-7.7 (2H, m)

MASS (m/z): 461.53 ( $\text{M}^+ + 1$ )

Preparation 157

4-[4-(5-Methoxypentyloxy)-1-piperidyl]benzohydrazide

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.30-1.80 (8H, m), 1.85-2.05 (2H, m), 3.00-3.18 (2H, m), 3.33 (3H, s), 3.34-3.60 (5H, m), 3.60-3.70 (2H, m), 3.95-4.15 (2H, m), 6.88 (2H, d,  $J=8.95\text{Hz}$ ), 7.53 (1H, s), 7.65 (2H, d,  $J=8.91\text{Hz}$ )

ESI MASS (m/z) (Positive): 358.4 ( $\text{M}^+ + \text{Na}$ )

Preparation 158

4-[4-(6-Methoxyhexyloxy)-1-piperidyl]benzohydrazide

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.3-2.1 (12H, m), 3.0-3.2 (2H, m), 3.33 (3H, s), 3.3-3.5 (5H, m), 3.5-3.8 (2H, m), 4.07 (2H, br s), 6.8-6.9 (2H, m), 7.36 (1H, br s), 7.6-7.7 (2H, m)

(+) APCI MASS (m/z) (Positive): 350.07 ( $\text{M}^+ + 1$ )

Preparation 159

4-[4-(4-Methoxybutoxymethyl)-1-piperidyl]benzohydrazide

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.2-1.9 (9H, m), 2.7-2.9 (2H, m), 3.2-3.5 (6H, m), 3.33 (3H, s), 3.7-3.9 (2H, m), 4.06 (2H, br s), 6.8-7.0 (2H, m), 7.30 (1H, br s), 7.6-7.7 (2H, m)

(+) APCI MASS (m/z) (Positive): 335.93 ( $\text{M}^+ + 1$ )

Preparation 160

4-[4-(5-Methoxypentyloxymethyl)-1-piperidyl]-benzohydrazide

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.2-2.0 (11H, m), 2.7-2.9 (2H, m), 3.2-3.5 (6H, m), 3.33 (3H, s), 3.8-4.2 (4H, m), 6.88 (2H, d, J=9.0Hz), 7.34 (1H, br s), 7.6-7.7 (2H, m)  
(+) APCI MASS (m/z) (Positive): 349.93 (M<sup>+</sup>+1)

5

Preparation 161

6-[4-(4-Methylcyclohexyl)-1-piperazinyl]-  
nicotinohydrazide

10 NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.94 (3H, d, J=6.9Hz), 1.4-2.0 (9H, m), 2.1-2.3 (1H, m), 2.5-2.7 (4H, m), 3.6-3.8 (4H, m), 3.9-4.3 (2H, m), 6.61 (1H, d, J=9.0Hz), 7.43 (1H, br s), 7.86 (1H, dd, J=9.0 and 2.5Hz), 8.54 (1H, d, J=2.3Hz)  
(+) APCI MASS (m/z) (Positive): 318.00 (M<sup>+</sup>+1)

15

Preparation 162

6-[4-(Trans-4-methylcyclohexyl)-1-piperazinyl]-  
nicotinohydrazide

20 NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.88 (3H, d, J=6.4Hz), 0.9-2.0 (9H, m), 2.2-2.4 (1H, m), 2.6-2.8 (4H, m), 3.5-3.7 (4H, m), 3.9-4.3 (2H, m), 6.61 (1H, d, J=9.1Hz), 7.33 (1H, br s), 7.85 (1H, dd, J=9.0 and 2.5Hz), 8.53 (1H, d, J=2.3Hz)  
(+) APCI MASS (m/z) (Positive): 318.00 (M<sup>+</sup>+1)

25

Preparation 163

6-[4-(4-Ethylcyclohexyl)-1-piperazinyl]-  
nicotinohydrazide

30 NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.8-1.0 (5H, m), 1.2-2.0 (9H, m), 2.2-2.4 (1H, m), 2.5-2.7 (4H, m), 3.5-3.7 (4H, m), 3.8-4.2 (2H, m), 6.61 (1H, d, J=9.0Hz), 7.38 (1H, br s), 7.86 (1H, dd, J=9.0 and 2.5Hz), 8.54 (1H, d, J=2.4Hz)  
(+) APCI MASS (m/z) (Positive): 332.00 (M<sup>+</sup>+1)

35 Preparation 164

6-[4-(Trans-4-ethylcyclohexyl)-1-piperazinyl]-nicotinohydrazide

NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.8-2.0 (14H, m), 2.2-2.4 (1H, m), 2.5-2.7 (4H, m), 3.5-3.7 (4H, m), 3.8-4.2 (2H, m), 6.61 (1H, d, J=9.0Hz), 7.32 (1H, br s), 7.86 (1H, dd, J=9.0 and 2.5Hz), 8.53 (1H, d, J=2.4Hz)

(+) APCI MASS (m/z) (Positive): 331.93 (M<sup>+</sup>+1)

#### Preparation 165

10 A mixture of methyl 4-[2-[4-(4-(7-methoxyheptyloxy)-cyclohexyl-1-piperazinyl]benzoyl]hydrazinocarbonyl]benzoate (1.9 g) and phosphorus pentasulfide (1.1 g) in ethylene glycol dimethyl ether (40 ml) was refluxed for 1.5 hours. After being  
15 added triethylamine, the reaction mixture was successively refluxed for 1.5 hours. After being cooled to room temperature, the reaction mixture was poured into ice-water. Then the solution was adjusted to pH 8 with 1N aqueous sodium hydroxide. The resulting precipitate was collected by filtration and washed  
20 with water to give methyl 4-[5-[4-[4-(7-methoxyheptyloxy)cyclohexyl-1-piperazinyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoate (2.13 g).

IR (KBr): 2931, 2856, 1718, 1606, 1439, 1281, 1111, 953 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 1.0-2.2 (19H, m), 2.8-3.6 (13H, m), 3.21 (3H, s), 3.90 (3H, s), 7.0-8.3 (8H, m)

25 ESI MASS (m/z) (Positive): 607.4 (M<sup>+</sup>+1)

The following compounds [Preparations 166 to 168] were obtained according to a similar manner to that of Preparation 165.

#### Preparation 166

Methyl 4-[5-[4-[4-(4-methylenecyclohexyl)-1-piperazinyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoate

IR (KBr): 3423, 2939, 2829, 1719, 1603, 1439 cm<sup>-1</sup>

35 NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 1.20-2.00 (6H, m), 2.10-2.40 (2H, m),

2.50-2.70 (4H, m), 3.15-3.30 (4H, m), 3.90 (7H, s),  
4.62 (1H, br s), 7.08 (2H, d,  $J=8.4\text{Hz}$ ), 7.85 (2H, d,  
 $J=9.3\text{Hz}$ ), 7.80-8.30 (4H, m)

MASS (m/z): 477 ( $M^++1$ ), 476 (M), 475 ( $M^+$ )

5

#### Preparation 167

4-[5-[4-[4-(8-Methoxyoctyloxy)cyclohexyl-1-piperazinyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoate

IR (KBr): 2929, 2854, 1724, 1606, 1439, 1281, 1111, 955  $\text{cm}^{-1}$

10 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.1-2.2 (21H, m), 2.8-3.6 (13H, m), 3.20 (3H, s), 3.8-3.9 (3H, m), 7.0-8.3 (8H, m)

ESI MASS (m/z) (Positive): 621.5 ( $M^++1$ )

#### Preparation 168

15 Methyl 4-[5-[4-[4-(5-methoxy-pentyloxy)-1-piperidyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoate

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.00-1.60 (8H, m), 1.80-1.95 (2H, m),  
2.75-2.95 (2H, m), 3.21 (3H, s), 3.55-3.75 (7H, m),  
3.90 (3H, s), 7.09 (2H, d,  $J=8.80\text{Hz}$ ), 7.84 (2H, d,  
20  $J=8.78\text{Hz}$ ), 8.13 (4H, s)

ESI MASS (m/z) (Positive): 518.2 ( $M^++\text{Na}$ )

#### Preparation 169

A mixture of 4-(1-cyclohexyl-4-piperidyl)benzonitrile  
25 (0.68 g), thiosemicarbazide (0.58g) and trifluoroacetic acid (3.5 ml) in toluene (7 ml) was stirred for 7 hours at 70°C. After being cooled to room temperature, the solvent was evaporated in vacuo. Then the residue was dissolved in tetrahydrofuran and poured into water. The solution was adjusted to pH 8 with 1N  
30 aqueous sodium hydroxide. The resulting precipitate was collected by filtration and washed with water and isopropyl ether to give 5-[4-(1-cyclohexyl-4-piperidyl)phenyl]-1,3,4-thiadiazol-2-amine trifluoroacetate (0.80 g).

IR (KBr): 3296, 2926, 1632, 1514, 1462  $\text{cm}^{-1}$

35 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.0-1.9 (14H, m), 2.2-2.6 (4H, m), 2.8-3.0

(2H, m), 7.2-7.4 (4H, m), 7.66 (2H, d, J=8.2Hz)  
(+) APCI MASS (m/z): 343.20 (M<sup>+</sup>+1)

The following compound was obtained according to a similar  
5 manner to that of Preparation 169.

#### Preparation 170

5-[4-[Cis-4-(4-methylcyclohexyl)piperazin-1-yl]phenyl]-  
[1,3,4]thiadiazol-2-ylamine  
10 NMR (CDCl<sub>3</sub>+CD<sub>3</sub>OD δ): 0.95 (3H, d, J=7.01Hz), 1.45-1.70 (8H,  
m), 1.70-1.85 (1H, m), 2.15-2.30 (1H, m), 2.65-2.80  
(4H, m), 3.25-3.35 (4H, m), 6.92 (2H, d, J=8.94Hz),  
7.64 (2H, d, J=8.85Hz)  
ESI MASS (m/z) (Positive): 358.4 (M<sup>+</sup>+1)

15

#### Preparation 171

A mixture of 5-[4-(1-cyclohexyl-4-piperidyl)phenyl]-  
1,3,4-thiadiazol-2-amine trifluoroacetate (0.78 g) and ethyl  
4-(bromoacetyl)benzoate (0.6 g) in ethanol (15 ml) was stirred  
20 for 5 hours at 80°C. After being cooled to room temperature,  
the reaction mixture was poured into isopropyl ether. The  
resulting precipitate was collected by filtration, washed with  
isopropyl ether and added to a solution of trifluoroacetic acid  
(1.5 ml) in xylene (15 ml). Then a mixture was stirred for 3  
25 hours at 130°C. After being cooled to room temperature, the  
reaction mixture was poured into isopropyl ether. The resulting  
precipitate was collected by filtration and washed with  
isopropyl ether to give ethyl 4-[2-[4-(1-cyclohexyl-4-  
piperidyl)phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-  
30 yl]benzoate trifluoroacetate (0.45 g).

IR (KBr): 2941, 1701, 1676, 1610, 1471, 1279, 1200, 1180,  
1132 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 1.0-2.2 (17H, m), 2.8-3.4 (4H, m), 3.4-3.6  
(2H, m), 3.8-4.5 (2H, m), 7.2-8.1 (8H, m), 8.94 (1H,  
35 s), 9.16 (1H, br s)

ESI MASS (m/z) (Positive): 515.3 ( $M^+ + 1$ )

The following compound was obtained according to a similar manner to that of Preparation 171.

5

Preparation 172

Ethyl 4-[2-[4-[cis-4-(4-methylcyclohexyl)-1-piperazinyl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoate bis(trifluoroacetate)

10 NMR ( $CDCl_3 + CD_3OD$ ,  $\delta$ ): 1.00 (3H, d,  $J = 7.13$ Hz), 1.42 (3H, t,  $J = 7.11$ Hz), 1.50-2.10 (10H, m), 2.90-3.20 (4H, m), 3.55-3.80 (4H, m), 4.39 (2H, q,  $J = 7.12$ Hz), 6.97 (2H, d,  $J = 8.89$ Hz), 7.78 (2H, d,  $J = 8.78$ Hz), 8.10 (2H, d,  $J = 8.42$ Hz), 8.11 (1H, s)

15 ESI MASS (m/z) (Positive): 529.7 ( $M^+ + 1$ )

Preparation 173

To a solution of benzyl 4-(trans-4-cyclohexylcyclohexyl)-1-piperazinecarboxylate (4 g) in ethanol (40 ml) and dioxane (40 ml) was added 10% palladium on carbon (0.8 g), and hydrogen gas at atmosphere pressure for 7 hours. To the reaction mixture was added dichloromethane (40 ml). The reaction mixture was filtered, and the filtrate was concentrated by evaporation under reduced pressure to give 1-(trans-4-cyclohexylcyclohexyl)piperazine (1.56 g).

25

IR (KBr): 1446, 1140, 835  $cm^{-1}$

NMR ( $CDCl_3$ ,  $\delta$ ): 0.75-1.35 (12H, m), 1.5-2.25 (9H, m), 2.54 (4H, t,  $J = 4.8$ Hz), 2.89 (4H, t,  $J = 4.8$ Hz)

MASS (m/z): 251 ( $M^+ + 1$ )

30

The following compound was obtained according to a similar manner to that of Preparation 173.

Preparation 174

35

1-(Trans-4-tert-butylcyclohexyl)piperazine

IR (KBr): 1450, 1365, 1140  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.84 (9H, s), 0.8-1.35 (5H, m), 1.7-2.25 (5H, m), 2.54 (4H, t,  $J=4.8\text{Hz}$ ), 2.89 (4H, t,  $J=4.9\text{Hz}$ )

MASS (m/z): 225 ( $M^+ + 1$ )

5

#### Preparation 175

To a mixture of cesium carbonate (2.54 g), palladium(II) acetate (62 mg) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (260 mg) in toluene (6 ml) was successively added  
10 methyl 4'-trifluoromethylsulfonyloxy-1,1'-biphenyl-4-carboxylate (1 g) and 1-(trans-4-cyclohexylcyclohexyl)-piperazine (835 mg) in stream of nitrogen. The mixture was stirred at ambient temperature for 45 minutes and at 110°C for  
15 further 23 hours. After cooling to room temperature, water and dichloromethane was added to the reaction mixture. The resulting precipitate was collected by filtration and washed with water and dried to give methyl 4'-[4-(trans-4-cyclohexylcyclohexyl)-1-piperazinyl]-1,1'-biphenyl-4-carboxylate (684.8 g).

20 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.8-2.4 (21H, m), 2.65-2.8 (4H, m), 3.2-3.4 (4H, m), 3.93 (3H, s), 6.99 (2H, d,  $J=8.8\text{Hz}$ ), 7.55 (2H, d,  $J=8.9\text{Hz}$ ), 7.62 (2H, d,  $J=8.4\text{Hz}$ ), 8.06 (2H, d,  $J=8.3\text{Hz}$ )

MASS (m/z): 461 ( $M^+ + 1$ )

25

The following compounds [Preparations 176 to 179] were obtained according to a similar manner to that of Preparation 175.

#### 30 Preparation 176

Methyl 4'-[4-(Trans-4-tert-butylcyclohexyl)-1-piperazinyl]-1,1'-biphenyl-4-carboxylate

35 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.86 (9H, s), 0.9-1.4 (5H, m), 1.75-2.4 (5H, m), 2.75 (4H, t,  $J=4.9\text{Hz}$ ), 3.28 (4H, t,  $J=4.9\text{Hz}$ ), 3.93 (3H, s), 7.00 (2H, d,  $J=8.8\text{Hz}$ ), 7.56 (2H, d,  $J=8.7\text{Hz}$ ),



7.62 (2H, d, J=8.4Hz), 8.06 (2H, d, J=8.3Hz)

MASS (m/z): 435 ( $M^+ + 1$ )

Preparation 177

- 5 tert-Butyl 4-(4'-methoxycarbonyl-1,1'-biphenyl-4-yl)-1-piperazinecarboxylate

NMR ( $CDCl_3$ ,  $\delta$ ): 1.49 (9H, s), 3.15-3.25 (4H, m), 3.55-3.65 (4H, m), 3.93 (3H, s), 6.99 (2H, d, J=6.8Hz), 7.5-7.65 (4H, m), 8.06 (2H, d, J=6.8Hz)

- 10 MASS (m/z): 396 ( $M^+ + 23$ )

Preparation 178

Methyl 4'-[4-(4-methoxyphenyl)-1-piperazinyl]-1,1'-biphenyl-4-carboxylate

- 15 NMR ( $CDCl_3$ ,  $\delta$ ): 3.2-3.35 (4H, m), 3.4-3.5 (4H, m), 3.79 (3H, s), 3.93 (3H, s), 6.8-7.1 (6H, m), 7.5-7.7 (4H, m), 8.07 (2H, d, J=8.3Hz)

MASS (m/z): 403 ( $M^+ + 1$ )

- 20 Preparation 179

Methyl 4'-[4-(4,4-dimethylcyclohexyl)-1-piperazinyl]-1,1'-biphenyl-4-carboxylate

- 25 NMR ( $CDCl_3$ ,  $\delta$ ): 0.92 (6H, s), 1.1-1.85 (8H, m), 2.1-2.3 (1H, m), 2.7-2.85 (4H, m), 3.2-3.4 (4H, m), 3.93 (3H, s), 7.00 (2H, d, J=8.8Hz), 7.56 (2H, d, J=8.8Hz), 7.62 (2H, d, J=8.4Hz), 8.06 (2H, d, J=8.4Hz)

MASS (m/z): 407 ( $M^+ + 1$ )

Preparation 180

- 30 To a solution of 2-(hydroxymethyl)-1,3-propanediol (3.0 g) and dimethoxymethylbenzene (6.36 ml) in DMF (50 ml) was added D-10-camphorsulfonic acid (1.31 g), and the mixture was stirred at ambient temperature overnight. To a reaction mixture were added triethylamine (1.18 ml) and water (150 ml) and the solution  
35 was extracted twice with ethyl acetate (150 ml). The extracts

were washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (200 ml) eluting with a mixture of hexane and ethyl acetate (1:1 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give (2-phenyl-1,3-dioxan-5-yl)methanol (4.51 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 3.43, 3.46 (1H, each s), 3.68-3.79 (2H, m), 4.00, 4.04 (1H, each s), 4.10-4.27 (3H, m), 5.41, 5.51 (1H, each s), 7.30-7.50 (5H, m)

#### Preparation 181

To a solution of (2-phenyl-1,3-dioxan-5-yl)methanol (2.0 g) in dichloromethane (40 ml) were added pyridinium chlorochromate (11.6 g) and molecular sieves 4A powder (5.0 g) with stirring and the mixture was stirred at ambient temperature for 5 hours. To a reaction mixture was added dichloromethane (100 ml) and the insoluble material was filtered off with celite and the filtrates were washed in turn with water, saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo to give 2-phenyl-1,3-dioxane-5-carbaldehyde (0.52 g). This compound was immediately used as the starting compound for the next step.

#### Preparation 182

Anhydrous cerium(III) chloride (10.0 g) was added to THF (100 ml) with stirring under ice-cooling and a mixture was stirred at ambient temperature overnight and then cooled in an ice bath. A solution of cyclohexyl magnesium chloride (2M solution in diethyl ether) (20.3 ml) was dropwise added to the mixture with stirring on ice bath (keeping the temperature below 6°C). To the mixture was added dropwise a solution of tert-butyl 4-oxo-1-piperidinecarboxylate (5.38 g) in THF (25 ml) and the mixture was stirred at 0-6°C for 1 hour. 10% aqueous acetic acid (100 ml) was added to the reaction mixture and extracted

twice with ethyl acetate (100 ml). The extracts were collected, washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (400 ml) eluting with a mixture of n-hexane and ethyl acetate (2:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give tert-butyl 4-cyclohexyl-4-hydroxy-1-piperidinecarboxylate (7.27 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.90-1.30 (5H, m), 1.46 (10H, s), 1.49-1.90 (9H, m), 2.90-3.15 (2H, m), 3.50-3.70 (1H, m), 3.80-4.00 (2H, m)

ESI MASS (m/z) (Positive): 306.3 (M<sup>+</sup>+Na)

#### Preparation 183

To a solution of tert-butyl 4-cyclohexyl-4-hydroxy-1-piperidinecarboxylate (7.26 g) in DMF (70 ml) was added sodium hydride (60% in oil) (2.05 g) with stirring under ice-cooling. The mixture was stirred at ambient temperature for 1 hour. To the suspension was added methyl iodide (4.79 ml) and the mixture was stirred at ambient temperature overnight. The reaction mixture was poured into ice-water (300 ml) and extracted three times with ethyl acetate (200 ml). The extracts were collected, washed twice with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (400 ml) eluting with a mixture of n-hexane and ethyl acetate (4:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give tert-butyl 4-cyclohexyl-4-methoxy-1-piperidinecarboxylate (6.77 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.85-1.30 (5H, m), 1.45 (10H, s), 1.46-1.85 (9H, m), 2.85-3.10 (2H, m), 3.12 (3H, s), 3.80-3.95 (2H, m)

ESI MASS (m/z) (Positive): 320.3 (M<sup>+</sup>+Na)

#### Preparation 184

To a solution of tert-butyl 4-cyclohexyl-4-methoxy-1-piperidinecarboxylate (2.04 g) in a mixture of dichloromethane (40 ml) and anisole (5.2 ml) was dropwise added trifluoroacetic acid (10.6 ml) with stirring under ice-cooling. The mixture was stirred at ambient temperature for 1 hour and then concentrated in vacuo. The resulting residue was azeotropically distilled three times with toluene (20 ml) and dried in vacuo. The obtained residue was dissolved in DMSO (20 ml). To the solution were added ethyl 4-fluorobenzoate (2.60 g) and potassium carbonate (2.84 g) and the mixture was stirred at 140°C overnight. The reaction mixture was poured into water (100 ml) and extracted twice with ethyl acetate (80 ml). The extracts were collected, washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (9:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give ethyl 4-(4-cyclohexyl-4-methoxy-1-piperidyl)benzoate (1.81 g).

NMR (CDCl<sub>3</sub>, δ): 0.85-1.32 (5H, m), 1.36 (3H, t, J=6.80Hz), 1.50-1.90 (10H, m), 2.95-3.15 (2H, m), 3.16 (3H, s), 3.55-3.70 (2H, m), 4.32 (2H, q, J=7.12Hz), 6.86 (2H, d, J=9.12Hz), 7.90 (2H, d, J=9.08Hz)

ESI MASS (m/z) (Positive): 368.3 (M<sup>+</sup>+Na)

The following compound was obtained according to a similar manner to that of Preparation 152.

#### Preparation 185

4-(4-Cyclohexyl-4-methoxy-1-piperidyl)benzohydrazide

NMR (CDCl<sub>3</sub>, δ): 0.9-1.9 (15H, m), 3.0-3.2 (2H, m), 3.16 (3H, s), 3.5-3.7 (2H, m), 4.06 (2H, br s), 6.8-7.0 (2H, m), 7.33 (1H, br s), 7.6-7.7 (2H, m)

(+) APCI MASS (m/z) (Positive): 332.40 (M<sup>+</sup>+1)

The following compound was obtained according to a similar manner to that of Preparation 32.

Preparation 186

- 5 Methyl 4-[2-[4-(4-cyclohexyl-4-methoxy-1-piperidyl)benzoyl]hydrazinocarbonyl]benzoate
- NMR (CDCl<sub>3</sub>,  $\delta$ ): 0.9-2.0 (15H, m), 3.0-3.2 (2H, m), 3.17 (3H, s), 3.5-3.8 (2H, m), 3.95 (3H, s), 6.8-7.0 (2H, m), 7.6-7.8 (2H, m), 7.8-8.0 (2H, m), 8.0-8.2 (2H, m), 9.1-9.2 (1H, m), 9.5-9.7 (1H, m)
- 10 (+) APCI MASS (m/z) (Positive): 494.47 (M<sup>+</sup>+1)

The following compound was obtained according to a similar manner to that of Preparation 47.

15

Preparation 187

- Methyl 4-[5-[4-(4-cyclohexyl-4-methoxy-1-piperidyl)phenyl]-1,3,4-thiadiazol-2-yl]benzoate
- ESI MASS (m/z) (Positive): 492.3 (M<sup>+</sup>+1)
- 20

The following compound was obtained according to a similar manner to that of Preparation 82.

Preparation 188

- 25 4-[5-[4-(4-Cyclohexyl-4-methoxy-1-piperidyl)phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid
- NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 0.8-1.8 (15H, m), 2.9-3.2 (5H, m), 3.6-3.8 (2H, m), 6.9-7.2 (2H, m), 7.7-8.3 (6H, m)
- ESI MASS (m/z) (Negative): 476.1 (M<sup>-</sup>-1)
- 30

The following compound was obtained according to a similar manner to that of Preparation 112.

Preparation 189

- 35 1-4-[5-[4-(4-Cyclohexyl-4-methoxy-1-piperidyl)phenyl]-

1,3,4-thiadiazol-2-yl]benzoyloxy-1H-1,2,3-benzotriazole

IR (KBr): 2927, 1784, 1603, 1441, 1412, 1234, 1192, 1080,  
987  $\text{cm}^{-1}$

5 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 0.9-1.9 (15H, m), 3.0-3.3 (5H, m), 3.5-3.8  
(2H, m), 6.9-7.1 (2H, m), 7.4-7.7 (3H, m), 7.90 (2H,  
d,  $J=8.9\text{Hz}$ ), 8.1-8.3 (3H, m), 8.3-8.5 (2H, m)

ESI MASS ( $m/z$ ) (Negative): 476.1 ( $\text{M}^-$ -HOBT-1)

10 The Starting Compounds used and the Object Compounds  
obtained in the following Examples 1 to 95 are given in the table  
as below, in which the formulas of the starting compounds are  
in the upper column, and the formulas of the object compounds  
are in the lower column, respectively.

15

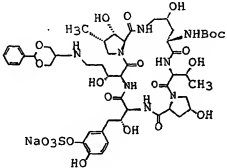
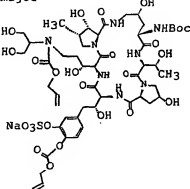
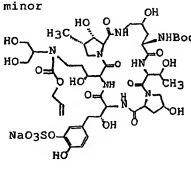
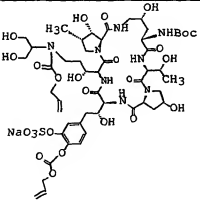
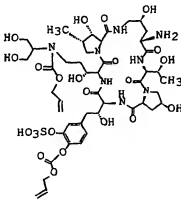
- to be continued on the next page -

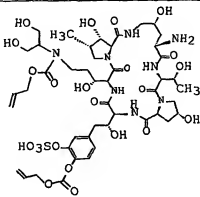
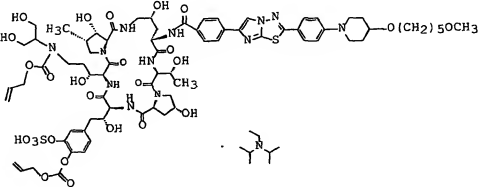
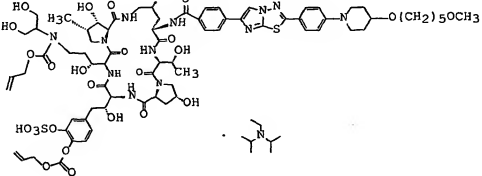
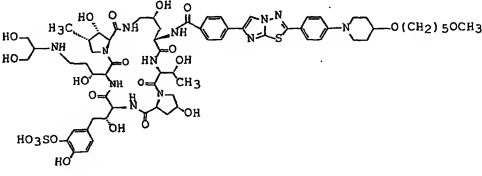
20

25

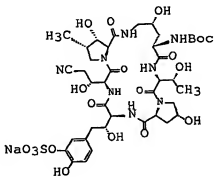
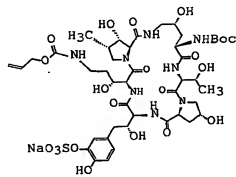
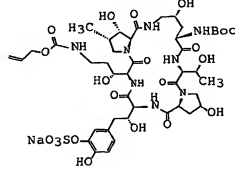
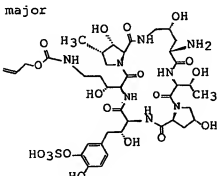
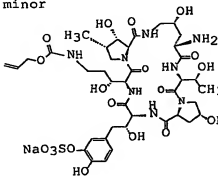
30

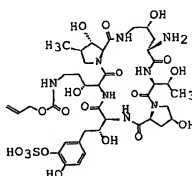
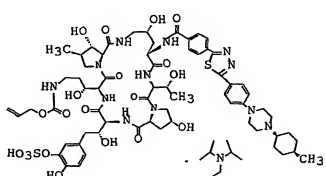
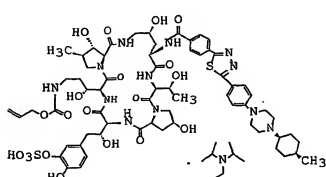
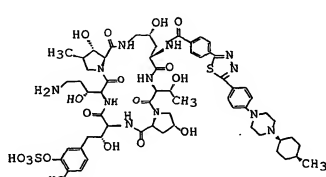
35

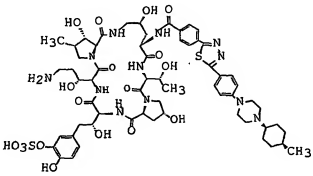
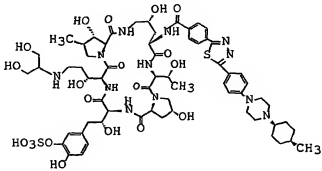
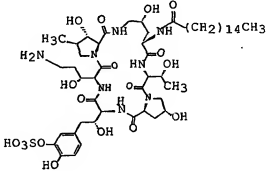
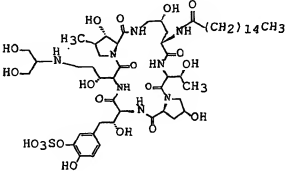
Example No.	Formula
1	
	<div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>major</p>  </div> <div style="text-align: center;"> <p>minor</p>  </div> </div>
2	
	

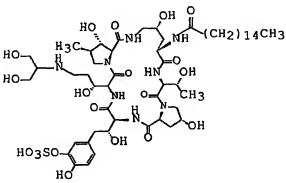
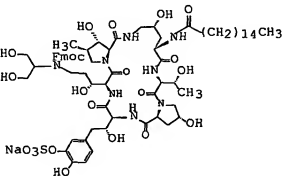
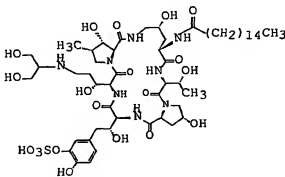
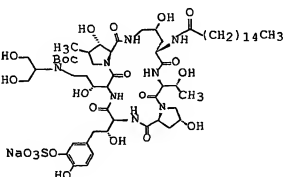
Example No.	Formula
3	
	
4	
	

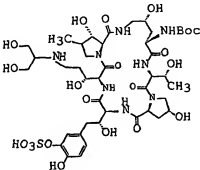
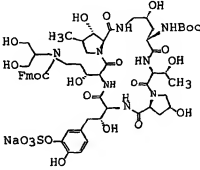
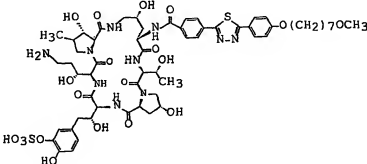
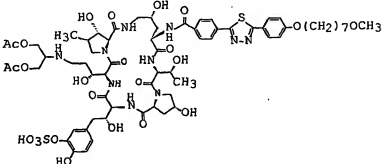


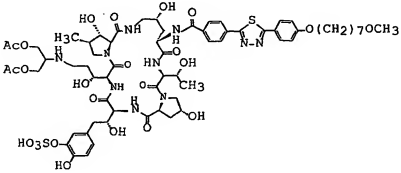
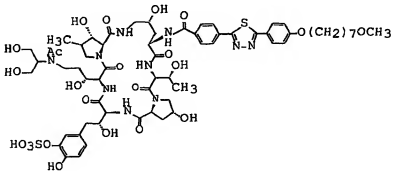
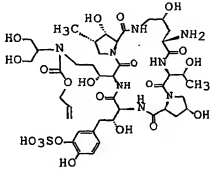
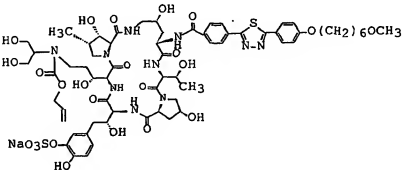
Example No.	Formula
5	
	
6	
	<div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>major</p>  </div> <div style="text-align: center;"> <p>minor</p>  </div> </div>

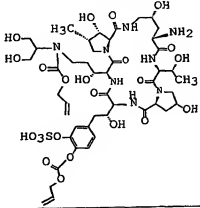
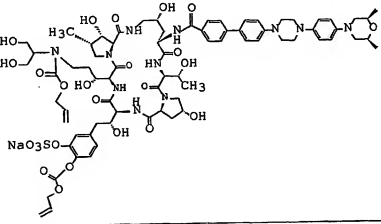
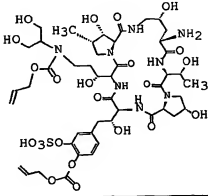
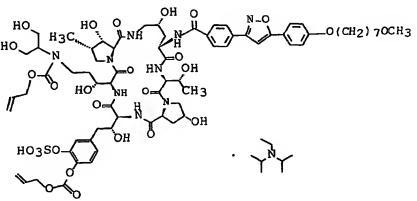
Example No.	Formula
7	
	
8	
	

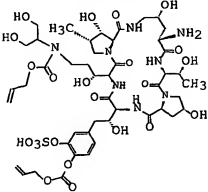
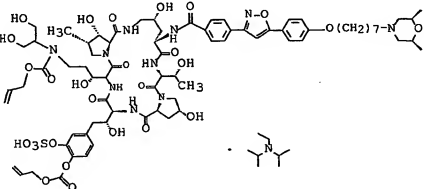
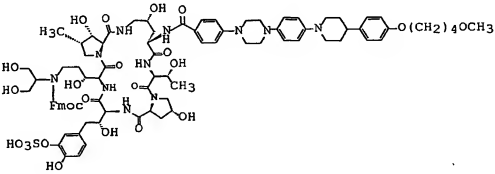
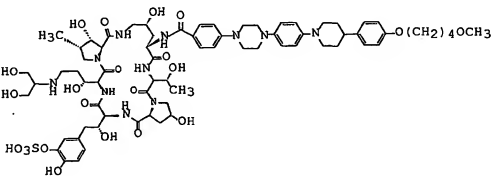
Example No.	Formula
9	
	
10	
	

Example No.	Formula
11	
	
12	
	

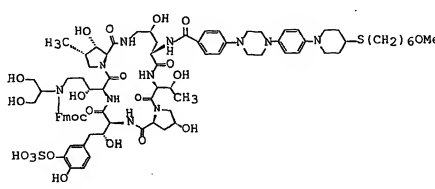
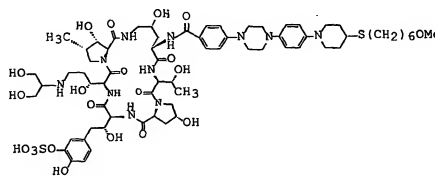
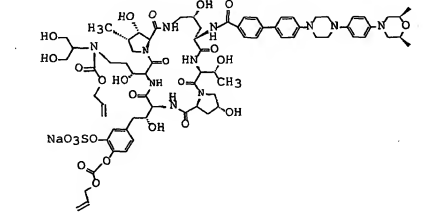
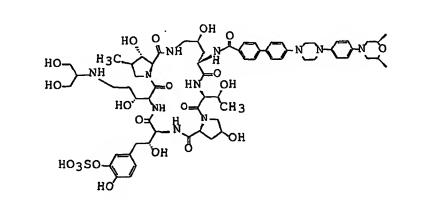
Example No.	Formula
13	
	
14	
	

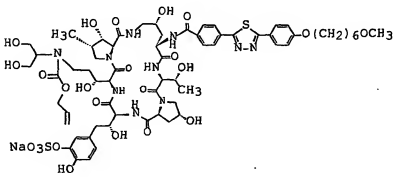
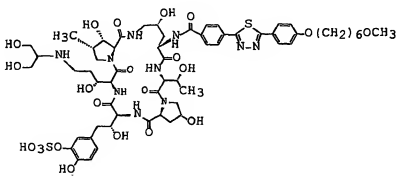
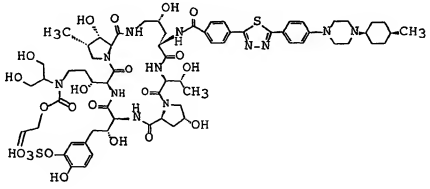
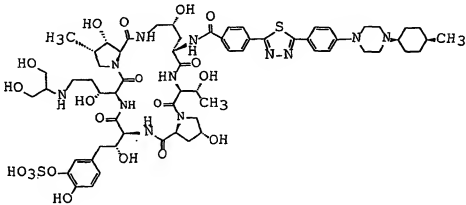
Example No.	Formula
15	 <p>Chemical structure of a complex molecule. It features a central core with multiple sugar units (pyranose and furanose rings) linked by glycosidic bonds. A sulfonamide group (SO<sub>2</sub>NH<sub>2</sub>) is attached to one of the sugar units. A long alkoxy chain (O(CH<sub>2</sub>)<sub>7</sub>OCH<sub>3</sub>) is attached to the sulfonamide group. The molecule also contains several hydroxyl groups and a methyl group.</p>
	 <p>Chemical structure of a complex molecule, similar to the one above. It features a central core with multiple sugar units (pyranose and furanose rings) linked by glycosidic bonds. A sulfonamide group (SO<sub>2</sub>NH<sub>2</sub>) is attached to one of the sugar units. A long alkoxy chain (O(CH<sub>2</sub>)<sub>7</sub>OCH<sub>3</sub>) is attached to the sulfonamide group. The molecule also contains several hydroxyl groups and a methyl group.</p>
16	 <p>Chemical structure of a complex molecule. It features a central core with multiple sugar units (pyranose and furanose rings) linked by glycosidic bonds. A sulfonamide group (SO<sub>2</sub>NH<sub>2</sub>) is attached to one of the sugar units. A long alkoxy chain (O(CH<sub>2</sub>)<sub>6</sub>OCH<sub>3</sub>) is attached to the sulfonamide group. The molecule also contains several hydroxyl groups and a methyl group.</p>
	 <p>Chemical structure of a complex molecule, similar to the one above. It features a central core with multiple sugar units (pyranose and furanose rings) linked by glycosidic bonds. A sulfonamide group (SO<sub>2</sub>NH<sub>2</sub>) is attached to one of the sugar units. A long alkoxy chain (O(CH<sub>2</sub>)<sub>6</sub>OCH<sub>3</sub>) is attached to the sulfonamide group. The molecule also contains several hydroxyl groups and a methyl group.</p>

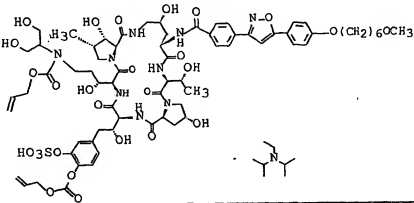
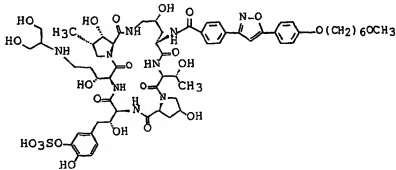
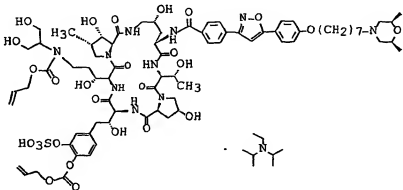
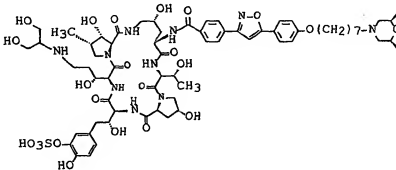
Example No.	Formula
17	
	
18	
	

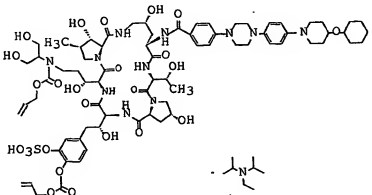
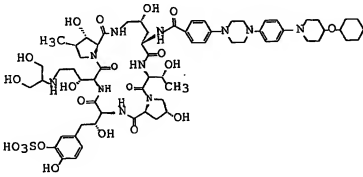
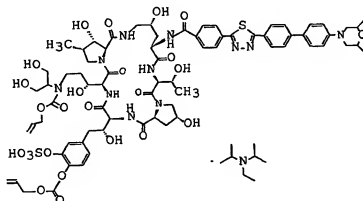
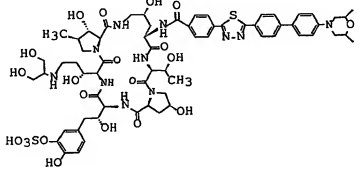
Example No.	Formula
19	
	
20	
	

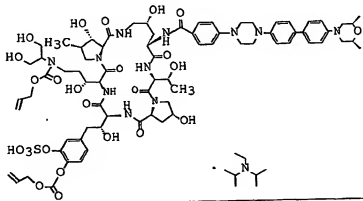
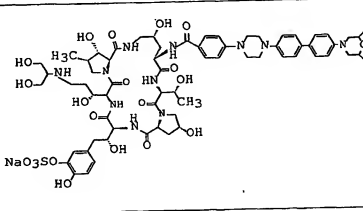
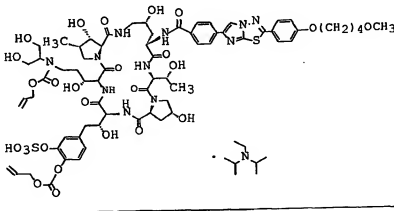
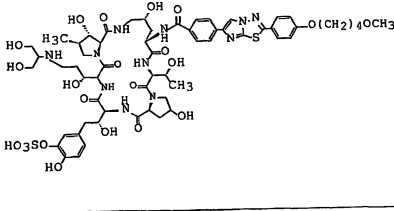


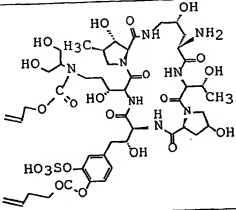
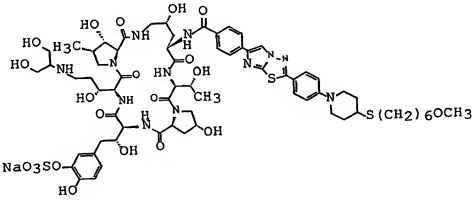
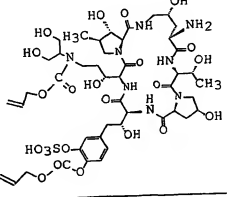
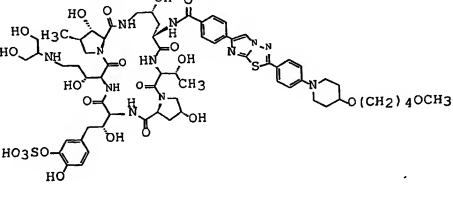
Example No.	Formula
21	
	
22	
	

Example No.	Formula
23	
	
24	
	

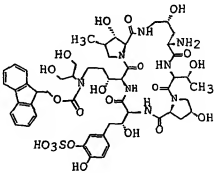
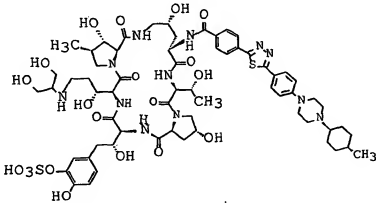
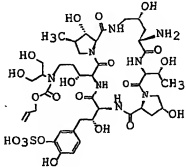
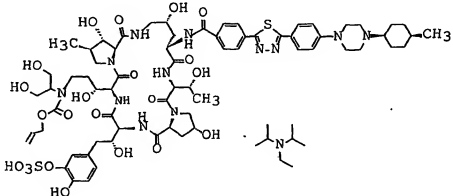
Example No.	Formula
25	
	
26	
	

Example No.	Formula
27	
	
28	
	

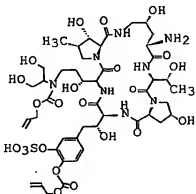
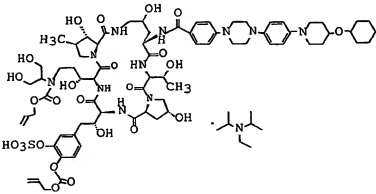
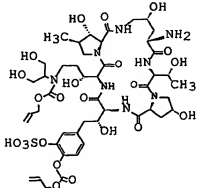
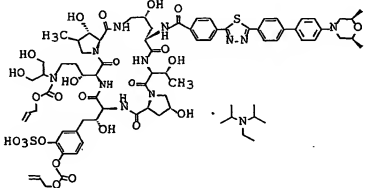
Example No.	Formula
29	
	
30	
	

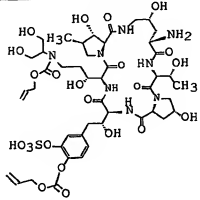
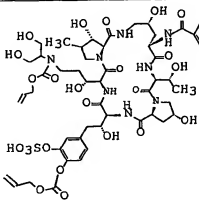
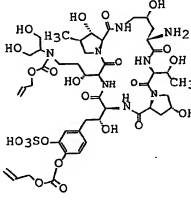
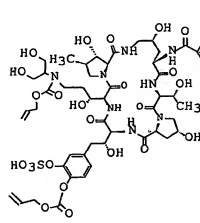
Example No.	Formula
31	
	
32	
	

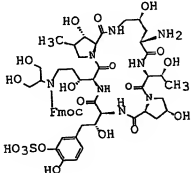
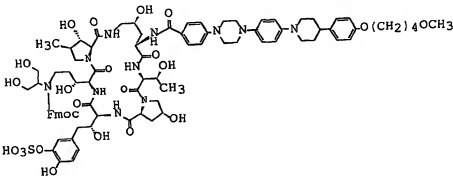
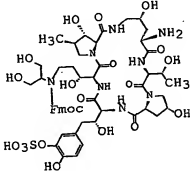
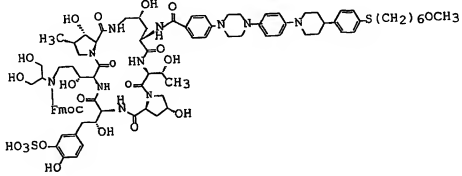
Example No.	Formula
33	
34	

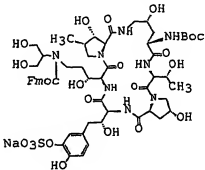
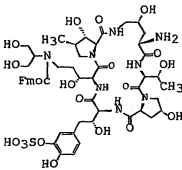
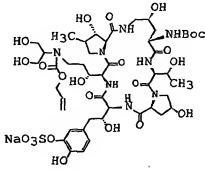
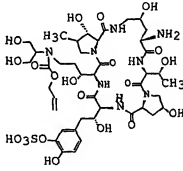
Example No.	Formula
35	
	
36	
	

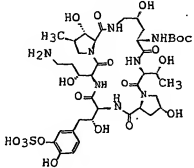
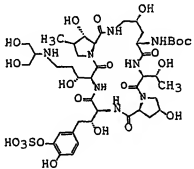
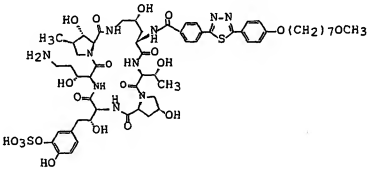
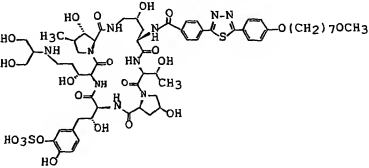


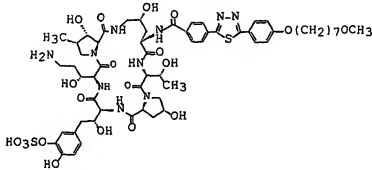
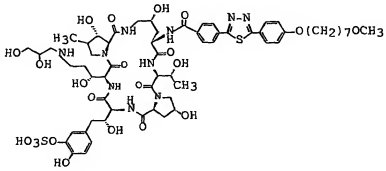
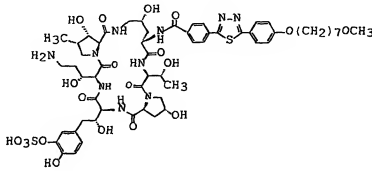
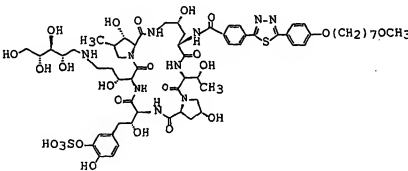
Example No.	Formula
37	
	
38	
	

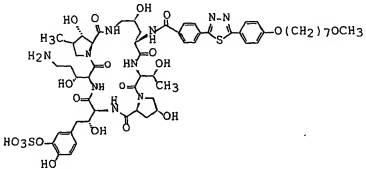
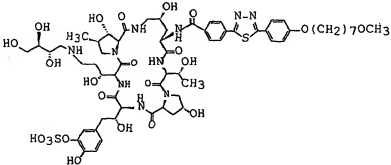
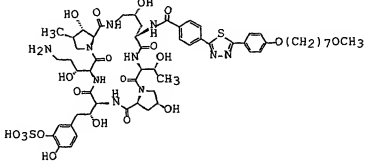
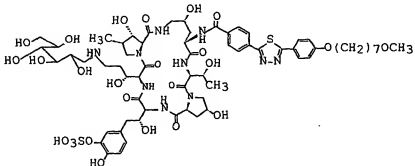
Example No.	Formula
39	
	
40	
	

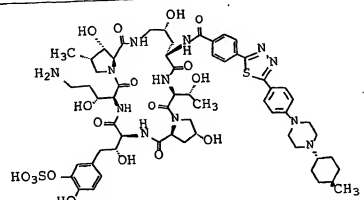
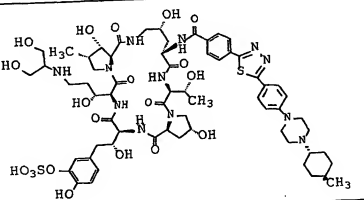
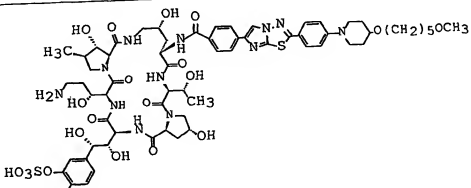
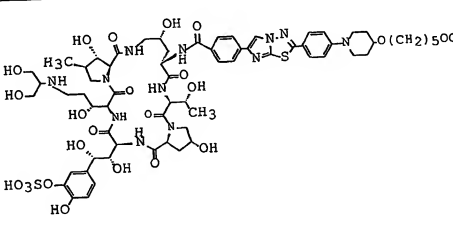
Example No.	Formula
41	
	
42	
	

Example No.	Formula
43	
	
44	
	

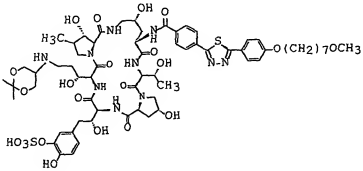
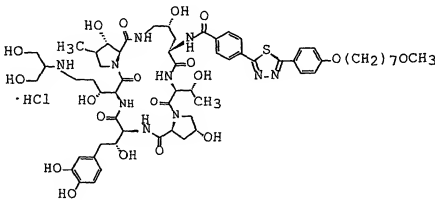
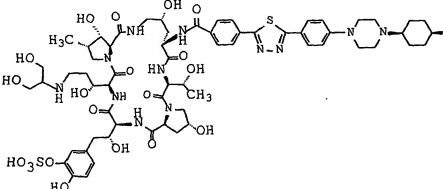
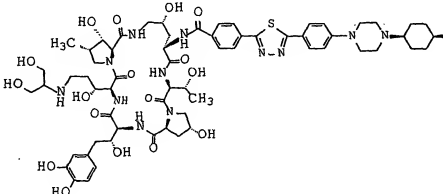
Example No.	Formula
45	
	
46	
	

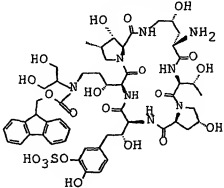
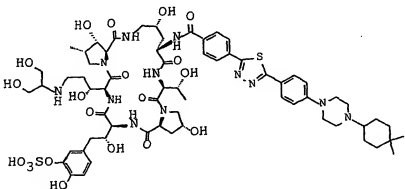
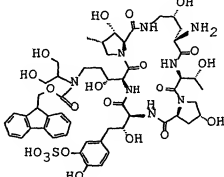
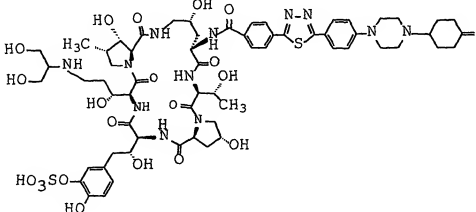
Example No.	Formula
47	
	
48	
	

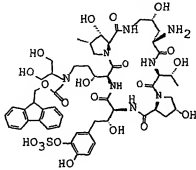
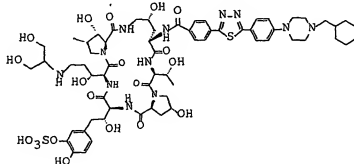
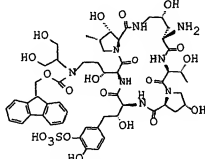
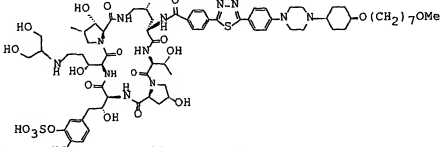
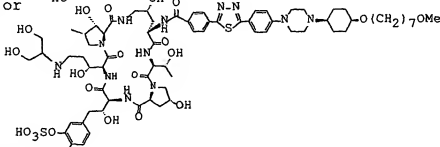
Example No.	Formula
49	
	
50	
	

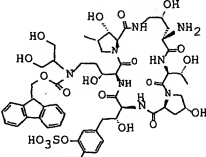
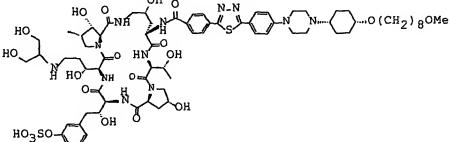
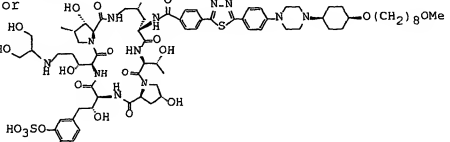
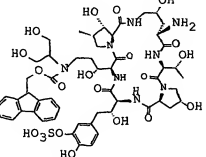
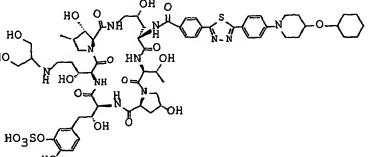
Example No.	Formula
51	
	
52	
	

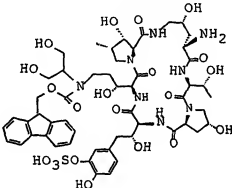
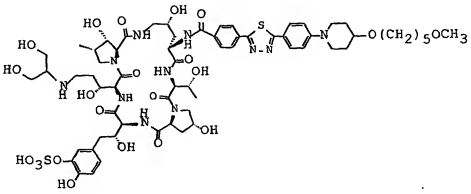
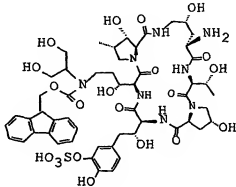
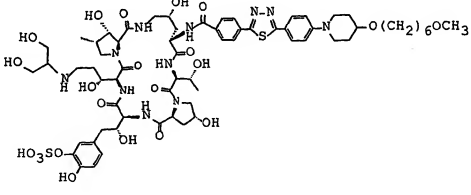


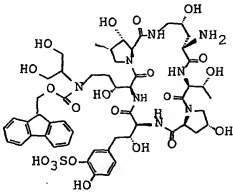
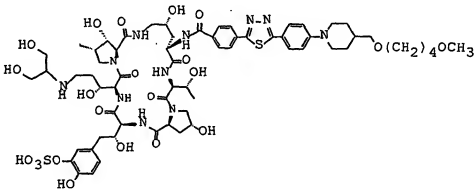
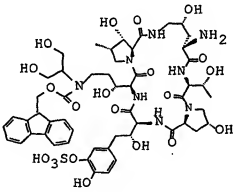
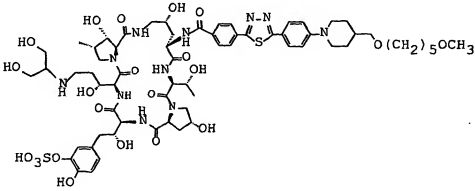
Example No.	Formula
53	
	
54	
	

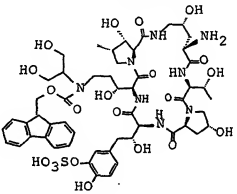
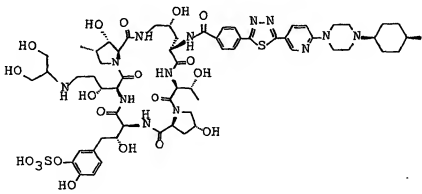
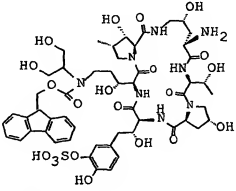
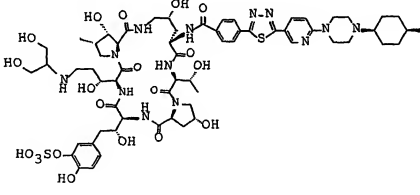
Example No.	Formula
55	
	
56	
	

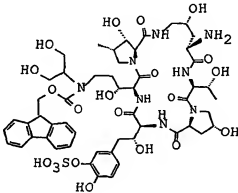
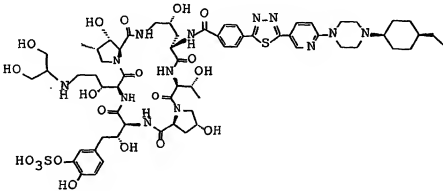
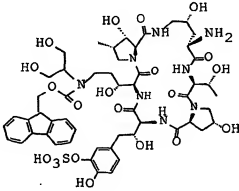
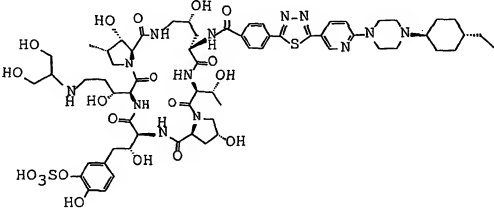
Example No.	Formula
57	
	
58	
	<p data-bbox="329 990 386 1010">Major</p>  <p data-bbox="329 1162 386 1181">Minor</p> 

Example No.	Formula
59	
	
	<p>Major</p>  <p>Minor</p>
60	
	

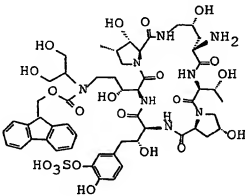
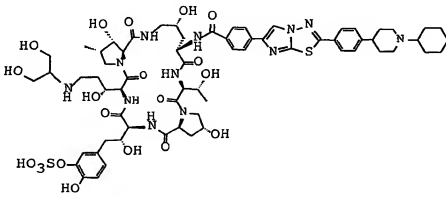
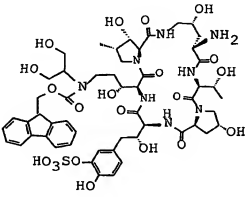
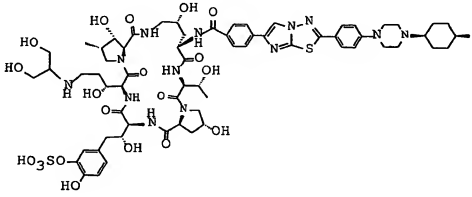
Example No.	Formula
61	
	
62	
	

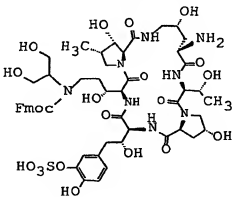
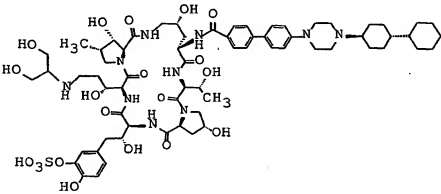
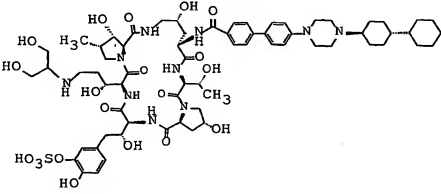
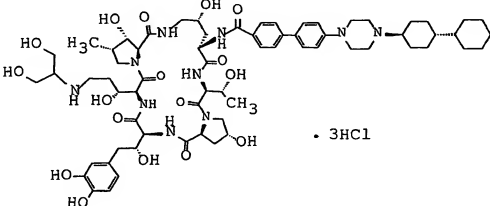
Example No.	Formula
63	
	
64	
	

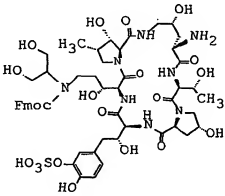
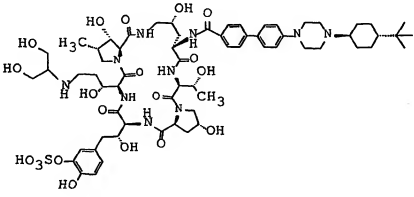
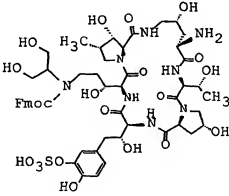
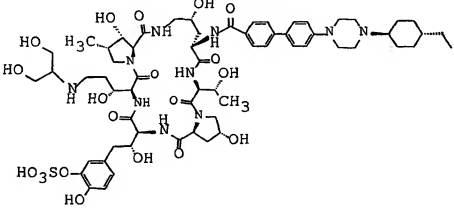
Example No.	Formula
65	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, amide bonds, and a sulfonate group (HO<sub>3</sub>SO-). The structure is highly branched and includes a naphthalene ring system.</p>
	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, amide bonds, and a sulfonate group (HO<sub>3</sub>SO-). The structure is highly branched and includes a naphthalene ring system.</p>
66	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, amide bonds, and a sulfonate group (HO<sub>3</sub>SO-). The structure is highly branched and includes a naphthalene ring system.</p>
	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, amide bonds, and a sulfonate group (HO<sub>3</sub>SO-). The structure is highly branched and includes a naphthalene ring system.</p>

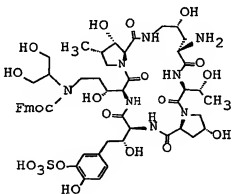
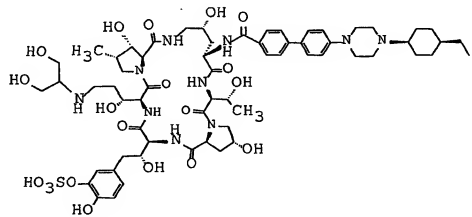
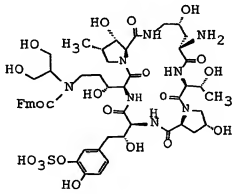
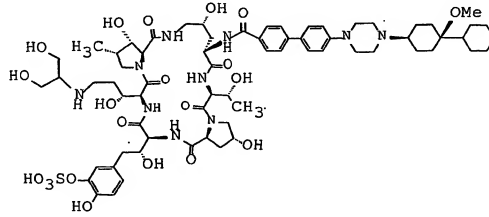
Example No.	Formula
67	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, amide bonds, and a sulfonate group (HO<sub>3</sub>SO-). The structure is highly branched and includes a naphthalene ring system.</p>
	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, amide bonds, and a sulfonate group (HO<sub>3</sub>SO-). The structure is highly branched and includes a naphthalene ring system.</p>
68	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, amide bonds, and a sulfonate group (HO<sub>3</sub>SO-). The structure is highly branched and includes a naphthalene ring system.</p>
	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, amide bonds, and a sulfonate group (HO<sub>3</sub>SO-). The structure is highly branched and includes a naphthalene ring system.</p>

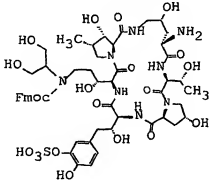
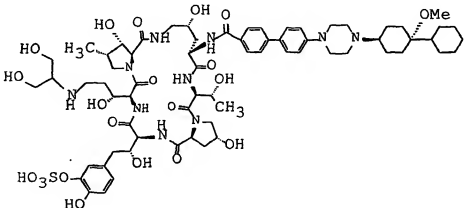
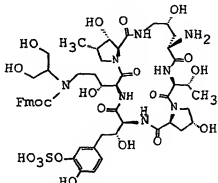
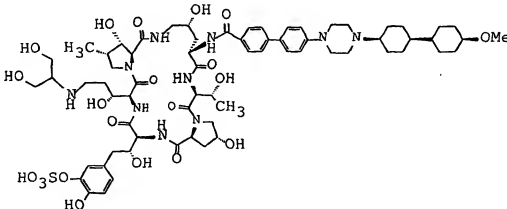


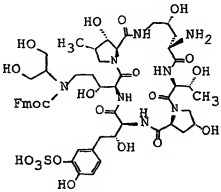
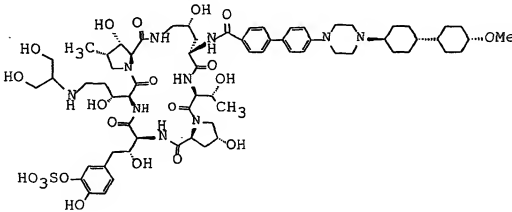
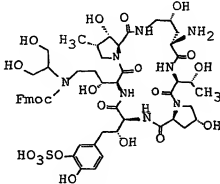
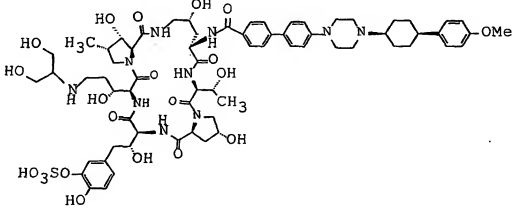
Example No.	Formula
69	 <p>Chemical structure of Example 69, top part: A complex molecule featuring a central core with multiple hydroxyl groups, a sulfonate group (HO<sub>3</sub>SO), and a phenyl ring. The structure is highly branched and includes several amide and ester linkages.</p>
	 <p>Chemical structure of Example 69, bottom part: A complex molecule featuring a central core with multiple hydroxyl groups, a sulfonate group (HO<sub>3</sub>SO), and a phenyl ring. The structure is highly branched and includes several amide and ester linkages.</p>
70	 <p>Chemical structure of Example 70, top part: A complex molecule featuring a central core with multiple hydroxyl groups, a sulfonate group (HO<sub>3</sub>SO), and a phenyl ring. The structure is highly branched and includes several amide and ester linkages.</p>
	 <p>Chemical structure of Example 70, bottom part: A complex molecule featuring a central core with multiple hydroxyl groups, a sulfonate group (HO<sub>3</sub>SO), and a phenyl ring. The structure is highly branched and includes several amide and ester linkages.</p>

Example No.	Formula
71	
	
72	
	 <p data-bbox="683 1072 751 1092">• 3HCl</p>

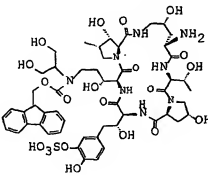
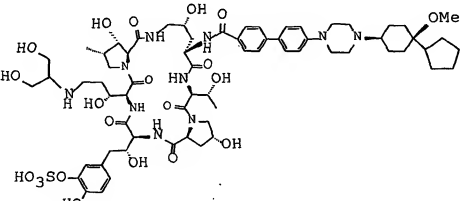
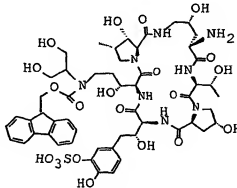
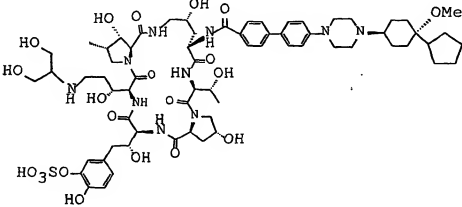
Example No.	Formula
73	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, an Fmoc-protected amine, and a sulfonate group (HO<sub>3</sub>SO-). The structure is highly branched and includes several amide and ester linkages.</p>
	 <p>Chemical structure of a complex molecule, similar to the one above, but with a different side chain. It features a central core with multiple hydroxyl groups, an Fmoc-protected amine, and a sulfonate group (HO<sub>3</sub>SO-). The structure is highly branched and includes several amide and ester linkages.</p>
74	 <p>Chemical structure of a complex molecule, similar to the one above, but with a different side chain. It features a central core with multiple hydroxyl groups, an Fmoc-protected amine, and a sulfonate group (HO<sub>3</sub>SO-). The structure is highly branched and includes several amide and ester linkages.</p>
	 <p>Chemical structure of a complex molecule, similar to the one above, but with a different side chain. It features a central core with multiple hydroxyl groups, an Fmoc-protected amine, and a sulfonate group (HO<sub>3</sub>SO-). The structure is highly branched and includes several amide and ester linkages.</p>

Example No.	Formula
75	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, an Fmoc group, and a sulfonate group. The structure is highly branched and contains several amide and ester linkages.</p>
	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, a sulfonate group, and a long chain with a piperazine ring. The structure is highly branched and contains several amide and ester linkages.</p>
76	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, an Fmoc group, and a sulfonate group. The structure is highly branched and contains several amide and ester linkages.</p>
	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, a sulfonate group, and a long chain with a piperazine ring and a methoxy group. The structure is highly branched and contains several amide and ester linkages.</p>

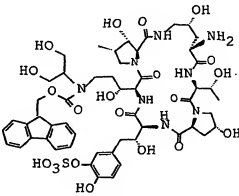
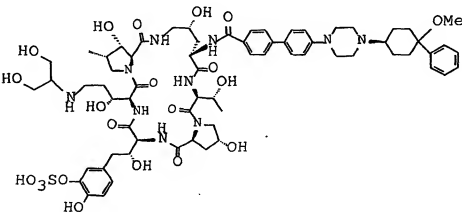
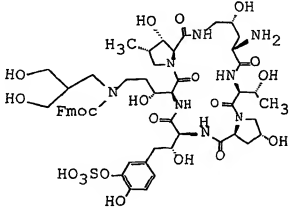
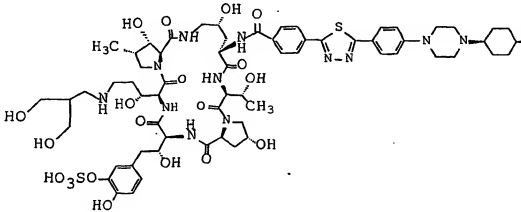
Example No.	Formula
77	
	
78	
	

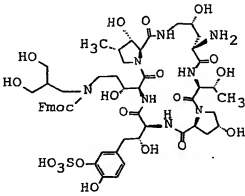
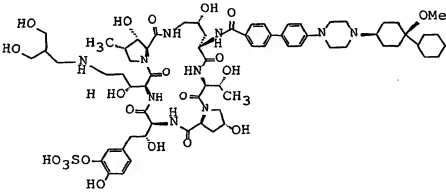
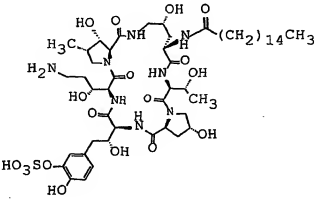
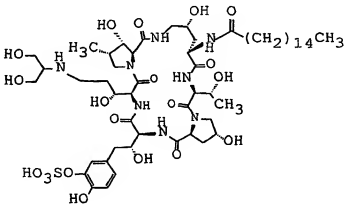
Example No.	Formula
79	 <p>Chemical structure of compound 79, top part: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, and a Fmoc-protected amine. It is linked via an amide bond to a side chain containing a 4-hydroxy-3-sulfamoylphenyl group.</p>
	 <p>Chemical structure of compound 79, bottom part: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, and a Fmoc-protected amine. It is linked via an amide bond to a side chain containing a 4-hydroxy-3-sulfamoylphenyl group and a long, flexible linker ending in a methoxy group.</p>
80	 <p>Chemical structure of compound 80, top part: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, and a Fmoc-protected amine. It is linked via an amide bond to a side chain containing a 4-hydroxy-3-sulfamoylphenyl group.</p>
	 <p>Chemical structure of compound 80, bottom part: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, and a Fmoc-protected amine. It is linked via an amide bond to a side chain containing a 4-hydroxy-3-sulfamoylphenyl group and a long, flexible linker ending in a methoxy group.</p>

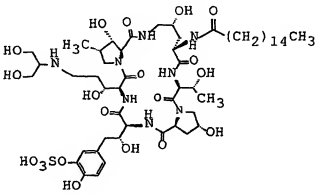
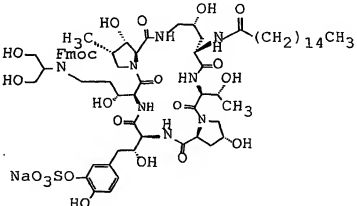
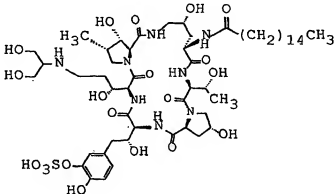
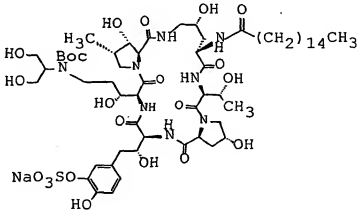


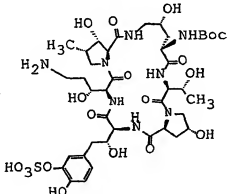
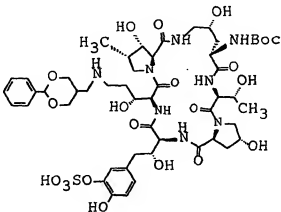
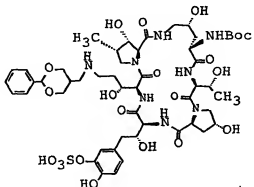
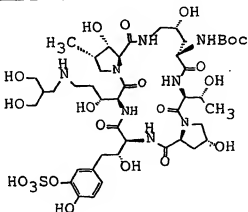
Example No.	Formula
83	
	
84	
	

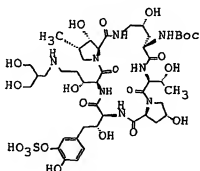
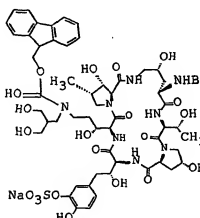
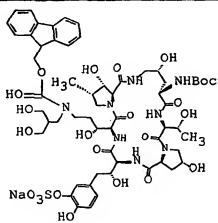
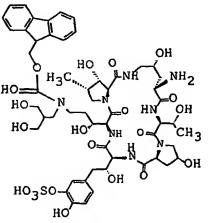


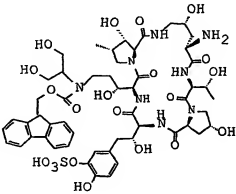
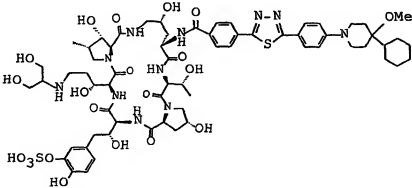
Example No.	Formula
85	
	
86	
	

Example No.	Formula
87	 <p>Chemical structure of a complex molecule featuring multiple hydroxyl groups, a sulfonate group (<math>\text{HO}_3\text{SO}</math>), and a Fmoc-protected amine group.</p>
	 <p>Chemical structure of a complex molecule featuring multiple hydroxyl groups, a sulfonate group (<math>\text{HO}_3\text{SO}</math>), and a long chain with a methoxy group (<math>\text{OMe}</math>).</p>
88	 <p>Chemical structure of a complex molecule featuring multiple hydroxyl groups, a sulfonate group (<math>\text{HO}_3\text{SO}</math>), and a long chain with a methyl group (<math>\text{CH}_3</math>).</p>
	 <p>Chemical structure of a complex molecule featuring multiple hydroxyl groups, a sulfonate group (<math>\text{HO}_3\text{SO}</math>), and a long chain with a methyl group (<math>\text{CH}_3</math>).</p>

Example No.	Formula
89	
	
90	
	

Example No.	Formula
91	
	
92	
	

Example No.	Formula
93	
	
94	
	

Example No.	Formula
95	
	

**Example 1**

A solution of the starting compound (1) (4.42 g) and 10% palladium on carbon (50% including water) (3.0 g) in a mixture of methanol (90 ml) and water (80 ml) was hydrogenated under an atmospheric pressure of hydrogen with stirring at ambient temperature for 8 hours. To the reaction mixture was added 10% palladium hydroxide on carbon (50% including water) (4.0 g), and the mixture was hydrogenated under an atmospheric pressure of hydrogen with stirring at ambient temperature for 16 hours. The catalyst was filtered off and washed with a mixture of methanol and water (1:1 v/v) (50 ml), and the filtrate and washes were combined. To the solution was dropwise added allyloxycarbonyl chloride (1.72 ml) in tetrahydrofuran (4 ml) adjusting to pH 8.5-10.0 with 1N sodium hydroxide with stirring on an ice-bath. The mixture was stirred at the same temperature for 2 hours and

adjusted to pH 8.0 with 1N hydrochloric acid. The solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (400 ml) eluting with 10% acetonitrile in water and then with 20%  
5 acetonitrile in water. The first fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the major object compound (1) (0.47 g). The second fractions  
10 containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the minor object compound (1) (2.91 g).

major object compound (1)

IR (KBr): 1761, 1672, 1635, 1512, 1450  $\text{cm}^{-1}$   
15 NMR ( $\text{DMSO}-d_6 + \text{D}_2\text{O}$ ,  $\delta$ ): 0.96 (3H, d,  $J=6.79\text{Hz}$ ), 1.00-1.15 (3H, m), 1.35 (9H, s), 1.45-2.50 (9H, m), 2.80-3.40 (6H, m), 3.70-4.60 (16H, m), 4.65-4.90 (4H, m), 5.10-5.45 (4H, m), 5.80-6.10 (2H, m), 6.71 (1H, d,  $J=8.23\text{Hz}$ ), 6.77 (1H, d,  $J=9.01\text{Hz}$ ), 6.98 (1H, s)  
20 ESI MASS (m/z) (Positive): 1277.2 ( $\text{M}^+ + \text{Na}$ )

minor object compound (1)

NMR ( $\text{DMSO}-d_6 + \text{D}_2\text{O}$ ,  $\delta$ ): 0.96 (3H, d,  $J=6.57\text{Hz}$ ), 1.06 (3H, d,  $J=4.94\text{Hz}$ ), 1.36 (9H, s), 1.45-2.45 (8H, m),  
25 2.75-3.70 (9H, m), 3.75-4.60 (12H, m), 4.69 (2H, d,  $J=5.19\text{Hz}$ ), 4.70-4.90 (2H, m), 5.05-5.50 (3H, m), 5.80-6.10 (1H, m), 6.91 (1H, d,  $J=8.29\text{Hz}$ ), 7.10 (1H, d,  $J=8.31\text{Hz}$ ), 7.43 (1H, s)  
30 ESI MASS (m/z) (Positive): 1193.3 ( $\text{M}^+ + \text{Na}$ )

## Example 2

A suspension of the object compound (2) (1.73 g) in dichloromethane (40 ml) was stirred with cooling at 5°C and treated with triethylsilane (1.1 ml), followed by  
35 trifluoroacetic acid (3.19 ml) dropwise over 30 minutes. After

warming to room temperature, the clear solution was stirred for 2 hours, and then poured into a mixture of saturated aqueous sodium hydrogen carbonate (100 ml) and pH 6.86 standard buffer (100 ml). Organic solvent was removed by evaporation, and the remaining aqueous solution purified by ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (200 ml) column chromatography, eluting with aqueous acetonitrile (10-20%). The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (2) (1.10 g).

IR (KBr): 1761, 1668, 1647, 1539, 1512, 1437  $\text{cm}^{-1}$

NMR (DMSO- $d_6$  +  $D_2O$ ,  $\delta$ ): 0.95 (3H, d,  $J=6.77\text{Hz}$ ), 1.18 (3H, d,  $J=4.94\text{Hz}$ ), 1.40-2.40 (7H, m), 2.70-3.40 (4H, m), 3.60-4.60 (17H, m), 4.69 (2H, d,  $J=5.37\text{Hz}$ ), 4.70-4.90 (2H, m), 5.10-5.50 (4H, m), 5.80-6.20 (2H, m), 6.89 (1H, d), 7.08 (1H, d,  $J=8.21\text{Hz}$ )

ESI MASS (m/z) (Positive): 1155.4 ( $M^+Na$ )

Elemental Analysis Calcd. for  $C_{46}H_{68}N_8O_{23}S \cdot 4H_2O$ :

C 45.84, H 6.36, N 9.30

Found : C 45.85, H 6.33, N 9.16

### Example 3

A solution of the starting compound (3) (0.43 g) in dimethylformamide (4 ml) was treated with 4-[2-[4-[4-(5-methoxypentyloxy)piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]-thiadiazol-6-yl]benzoic acid benzotirazol-1-yl ester (194 mg) and diisopropylethylamine (78.4  $\mu\text{l}$ ) and stirred for 5 hours at room temperature. Ethyl acetate (50 ml) was added, and the resulting precipitate collected, washed with isopropyl ether, and dried to give the object compound (3) (610.6 mg) as a crude powder, that was used directly in the next reaction without purification.



Example 4

To a solution of the starting compound (4) (610.6 mg) in a mixture of methanol (10 ml) and tetrahydrofuran (25 ml) were successively added triphenylphosphine (32 mg),  
5 tetrakis(triphenylphosphine)palladium(0) (35 mg) and morpholine (106  $\mu$ l) with stirring, and the mixture was stirred at ambient temperature for 3.5 hours. Ethyl acetate (100 ml) was added, and the resulting precipitate collected, washed with isopropyl ether, and dried to give a crude pale yellow powder  
10 (535 mg). The crude powder was dissolved sodium hydroxide aqueous solution and subjected to column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark: prepared by YMC Co., Ltd.)) (37% acetonitrile aqueous solution). The fractions containing the object compound were combined, and evaporated under reduced  
15 pressure to remove acetonitrile. The residue was lyophilized to give the object compound (4) (293.7 mg).

IR (KBr): 3355.5, 1633.4, 1608.3, 1529.3, 1517.7, 1463.7, 1444.4, 1267.0, 1230.4  $\text{cm}^{-1}$

20 NMR (DMSO- $d_6$ ,  $\delta$ ): 0.98 (3H, d,  $J=6.7\text{Hz}$ ), 1.10 (3H, d,  $J=5.6\text{Hz}$ ), 1.2-5.6 (65H, m), 6.71 (1H, d,  $J=8.1\text{Hz}$ ), 6.78 (1H, d,  $J=9.7\text{Hz}$ ), 7.00 (1H, s), 7.09 (2H, d,  $J=9.1\text{Hz}$ ), 7.75 (2H, d,  $J=8.7\text{Hz}$ ), 7.95 (4H, s), 7.3-8.7 (7H, m), 8.79 (1H, s)

MASS (m/z): 1465.5 (M-H) $^{-}$

25 Elemental Analysis Calcd. for  $\text{C}_{66}\text{H}_{90}\text{N}_{12}\text{O}_{22}\text{S}_2 \cdot 7\text{H}_2\text{O}$ :

C 49.74, H 6.58, N 10.55

Found : C 49.72, H 6.43, N 10.40

Example 5

30 A solution of the starting compound (5) (10 g) in a mixture of methanol (500 ml) and water (100 ml) was treated with cobalt (II) chloride hexahydrate (9.43 g) and then stirred to give a pink solution. Sodium borohydride (7.5 g) was then added portionwise and stirred for 1 hour at ambient temperature. The  
35 reaction mixture was filtered through a bed of celite, washing

with a mixture of methanol (100 ml) and water (20 ml). The ice-cooled filtrate was then treated dropwise with a solution of allyloxycarbonyl chloride (1.46 ml) in tetrahydrofuran (10 ml), keeping pH 8.0-9.5 with 1N sodium hydroxide and then stirred for 1 hour at the same temperature. The reaction mixture was evaporated in vacuo (about 200 ml) and added 1N sodium hydroxide (60 ml), and then the mixture was stayed in the refrigerator overnight. To the solution was added water (200 ml), and the mixture was purified by ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (200 ml) column chromatography, eluting with aqueous acetonitrile (5-20%). The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (5) (8.58 g).

IR (KBr): 1670, 1633, 1516, 1443, 1269  $\text{cm}^{-1}$

NMR ( $\text{DMSO}-d_6 + \text{D}_2\text{O}$ ,  $\delta$ ): 0.97 (3H, d,  $J=6.75\text{Hz}$ ), 1.08 (3H, d,  $J=5.52\text{Hz}$ ), 1.35 (9H, s), 1.40-2.00 (6H, m), 2.10-2.50 (3H, m), 2.80-3.40 (4H, m), 3.65-4.50 (14H, m), 4.65-4.85 (2H, m), 5.05-5.35 (2H, m), 5.70-6.00 (1H, m), 6.72 (1H, d,  $J=8.12\text{Hz}$ ), 6.78 (1H, d,  $J=10.1\text{Hz}$ )

ESI MASS (m/z) (Positive): 1119.3 ( $\text{M}^+ + \text{Na}$ )

Elemental Analysis Calcd. for  $\text{C}_{45}\text{H}_{67}\text{N}_8\text{O}_{21}\text{SNa}\cdot 5\text{H}_2\text{O}$ :

C 44.52, H 6.37, N 9.44

Found : C 44.59, H 6.43, N 9.47

#### Example 6

A suspension of the starting compound (6) (8.5 g) in dichloromethane (180 ml) was stirred with cooling at 5°C and treated with triethylsilane (6.2 ml), followed by trifluoroacetic acid (17.9 ml) dropwise over 30 minutes. After warming to room temperature, the clear solution was stirred for 2 hours, then poured into a mixture of saturated aqueous sodium hydrogen carbonate (200 ml) and pH 6.86 standard buffer (200 ml). Organic solvent was removed by evaporation, and the remaining

aqueous solution purified by ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (200 ml) column chromatography, eluting with aqueous acetonitrile (5-20%). The fractions containing the object compound were collected and  
5 evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (6) (5.53 g).

10 NMR (DMSO- $d_6$  +  $D_2O$ ,  $\delta$ ): 0.97 (3H, d,  $J=6.64\text{Hz}$ ), 1.15 (3H, d,  $J=5.52\text{Hz}$ ), 1.30-1.70 (3H, m), 1.80-2.50 (6H, m), 2.70-4.00 (14H, m), 4.20-4.60 (8H, m), 4.70-4.90 (2H, m), 5.10-5.40 (2H, m), 5.70-6.10 (1H, m), 6.70-6.90 (2H, m), 7.06 (1H, s)

ESI MASS (m/z) (Positive): 997.3 ( $M^+$ +Na)

15 Example 7

A solution of the starting compound (7) (0.5 g) in dimethylformamide (10 ml) was treated with 4-[5-[4-[4-(cis-4-methylcyclohexyl)piperazinyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid benzotriazol-1-yl ester (0.3 g) and  
20 diisopropylethylamine (0.13 ml) and stirred for 20 hours at room temperature. Ethyl acetate (100 ml) was added and the resulting precipitate collected, washed with ethyl acetate, and dried to give the object compound (7) (0.5 g).

25 NMR (DMSO- $d_6$ ,  $\delta$ ): 0.90 (3H, d,  $J=6.8\text{Hz}$ ), 0.97 (3H, d,  $J=6.6\text{Hz}$ ), 1.13 (3H, d,  $J=5.0\text{Hz}$ ), 1.43-6.10 (78H, m), 6.69-8.72 (18H, m)

ESI MASS (m/z) (Negative): 1418.4 ( $M^+$ )

Example 8

30 To a suspension of the starting compound (8) (0.38 g) in a mixture of methanol (7.6 ml) and tetrahydrofuran (1.9 ml) were successively added triphenylphosphine (0.04 g), tetrakis(triphenylphosphine)palladium(0) (0.088 g) and morpholine (0.14 ml) with stirring and the mixture was stirred  
35 at ambient temperature for 15 hours. To the reaction mixture

- was added ethyl acetate (100 ml). The resulting precipitate was collected by filtration and dried in vacuo. The precipitate was dissolved in a mixture of water and 1N sodium hydroxide and the solution was subjected to column chromatography on ODS
- 5 (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (100 ml) eluting with 40% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (8) (0.25
- 10 g).
- NMR (DMSO- $d_6$ ,  $\delta$ ): 0.90 (3H, d, J=6.7Hz), 0.98 (3H, d, J=6.7Hz), 1.11 (3H, d, J=5.7Hz), 1.42-5.23 (56H, m), 6.69-8.92 (17H, m)
- ESI MASS (m/z) (Negative): 1334.4 ( $M^+$ )
- 15 Elemental Analysis Calcd. for  $C_{61}H_{82}N_{12}O_{18}S_2 \cdot 8H_2O$ :  
C 49.52, H 6.68, N 11.36  
Found : C 49.25, H 6.41, N 11.20

#### Example 9

- 20 The suspension of a mixture of the starting compound (9) (100 mg), 1,3-dihydroxyacetate (13.5 mg) and acetic acid (0.13 ml) in a mixture of methanol (1.5 ml) and dimethylformamide (0.7 ml) was added sodium cyanoborohydride (9.4 mg) with stirring at ambient temperature, and the mixture was stirred at the same
- 25 temperature overnight. To the reaction mixture was added ethyl acetate (20 ml). The resulting precipitate was collected by filtration and dried in vacuo. The precipitate was dissolved in a mixture of water and 1N sodium hydroxide and the solution was subjected to column chromatography on ODS (Daiso-gel,
- 30 SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (50 ml) eluting with 40% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (9) (55 mg).
- 35 NMR (DMSO- $d_6$ ,  $\delta$ ): 0.90 (3H, d, J=6.8Hz), 0.98 (3H, d,

J=6.7Hz), 1.11 (3H, d, J=5.5Hz), 1.43-5.24 (62H, m),  
6.69-8.85 (17H, m)

ESI MASS (m/z) (Negative): 1408.3 (M<sup>+</sup>)

5 Example 10

To a solution of a mixture of the starting compound (10) (7.5 g), 1,3-dihydroxyacetone (1.19 g) and acetic acid (1.14 ml) in a mixture of methanol (120 ml) and dimethylformamide (55 ml) was added sodium cyanoborohydride (835 mg) with stirring at ambient temperature, and the mixture was stirred at the same temperature overnight. To a reaction mixture was poured into ethyl acetate (700 ml). The resulting precipitates were collected by filtration, washed with ethyl acetate (100 ml) and dried in vacuo. The precipitates were dissolved in a mixture of 30% aqueous acetonitrile (800 ml) and 1N sodium hydroxide (5 ml). The solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (440 ml) eluting in turn with water and aqueous acetonitrile (30%-60%). The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (10) (5.22 g).

IR (KBr): 1632, 1535, 1518, 1443, 1269, 1082, 1047 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub> + D<sub>2</sub>O, δ): 0.82 (3H, d, J=6.83Hz), 0.97 (3H, d, J=6.81Hz), 1.02 (3H, d, J=6.18Hz), 1.24 (26H, s), 1.35-2.45 (14H, m), 2.75-3.40 (5H, m), 3.60-4.50 (15H, m), 4.7-4.90 (2H, m), 6.65-6.80 (2H, m), 7.01 (1H, s)

ESI MASS (m/z) (Positive): 1088.4 (M<sup>+</sup>+Na)

30 Example 11

To a solution of the starting compound (11) (4.0 g) in dimethylformamide (40 ml) were successively added diisopropylethylamine (1.45 ml) and 9-fluorenylmethyl chloroformate (1.03 g), and the mixture was stirred at ambient temperature for 2 hours. The reaction mixture was poured into

water (200 ml). The solution was purified by ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (200 ml) column chromatography, eluting in turn with a mixture of saturated aqueous sodium chloride (400 ml), saturated aqueous sodium hydrogen carbonate (50 ml) and water (400 ml), and aqueous acetonitrile (30-60%). The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (11) (2.82 g).

IR (KBr): 1666, 1632, 1518, 1446, 1273, 1246, 1082, 1047  $\text{cm}^{-1}$

NMR (DMSO- $d_6$  +  $D_2O$ ,  $\delta$ ): 0.80-1.10 (9H, m), 1.23 (26H, s), 1.35-2.45 (12H, m), 2.60-3.40 (6H, m), 3.60-4.55 (18H, m), 4.65-4.90 (2H, m), 6.65-6.85 (2H, m), 6.97 (1H, s), 7.30-7.50 (4H, m), 7.60-7.95 (4H, m)

ESI MASS (m/z) (Negative): 1423.7 ( $M^+ - Na$ )

Elemental Analysis Calcd. for  $C_{69}H_{99}N_8O_{22}SNa \cdot 6H_2O$ :

C 53.27, H 7.19, N 7.20

Found: C 53.45, H 7.21, N 7.10

20

#### Example 12

To a solution of the object compound (12) (1.21 g) in dimethylformamide (15 ml) were successively added diisopropylethylamine (0.26 ml) and di-tert-butyl dicarbonate (285 mg), and the mixture was stirred at ambient temperature overnight. The reaction mixture was poured into a mixture of pH 6.86 standard buffer solution (150 ml), saturated aqueous sodium chloride (50 ml) and saturated aqueous sodium hydrogen carbonate (20 ml). The mixture was purified by ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (200 ml) column chromatography, eluting with aqueous acetonitrile (30-50%). The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (12) (1.19 g).

35

IR (KBr): 1662, 1632, 1535, 1518, 1444, 1367, 1272,  
1250  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6 + \text{D}_2\text{O}$ ,  $\delta$ ): 0.85 (3H, d,  $J=6.76\text{Hz}$ ), 0.96 (3H, d,  
 $J=6.77\text{Hz}$ ), 1.04 (3H, d,  $J=5.50\text{Hz}$ ), 1.23 (26H, s), 1.37  
(9H, s), 1.40-1.50 (2H, m), 1.55-2.50 (10H, m),  
2.80-3.40 (6H, m), 3.50-4.45 (14H, m), 6.65-6.80 (2H,  
m), 6.96 (1H, s)

ESI MASS ( $m/z$ ) (Negative): 1301.6 ( $\text{M}^+ - \text{Na}$ )

10 Example 13

To a solution of a mixture of starting compound (13) (1.62 g) and diisopropylethylamine (0.58 ml) in DMF (16 ml) was added 9-fluorenylmethoxycarbonyl chloride (493 mg) with stirring at ambient temperature, and the mixture was stirred at the same  
15 temperature for 3 hours. The reaction mixture was poured into ethyl acetate (250 ml). To the mixtures was added pH 6.86 standard buffer solution (100 ml) and 5% aqueous sodium chloride (20 ml), and the aqueous layer was separated. The organic layer was extracted with 5% aqueous sodium chloride (100 ml), and these  
20 aqueous layers were collected and evaporated in vacuo to remove organic solvent. The solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (200 ml) eluting with 40% acetonitrile in water. The fractions containing the object  
25 compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (13) (1.38 g).

NMR ( $\text{DMSO-d}_6 + \text{D}_2\text{O}$ ,  $\delta$ ): 0.89 (3H, d,  $J=6.26\text{Hz}$ ), 1.09 (3H, broad s), 1.33 (9H, s), 1.40-2.10 (5H, m),  
30 2.10-2.35 (2H, m), 2.75-3.40 (5H, m), 3.50-4.50 (16H, m), 4.60-4.90 (2H, m), 6.65-6.80 (2H, m), 6.97 (1H, s), 7.25-7.50 (4H, m), 7.70 (2H, d,  $J=6.82\text{Hz}$ ), 7.88 (2H, d,  $J=6.77\text{Hz}$ )

ESI MASS ( $m/z$ ) (Positive): 1331.3 ( $\text{M}^+ + \text{Na}$ )

35 Elemental Analysis Calcd. for  $\text{C}_{58}\text{H}_{77}\text{N}_8\text{O}_{23}\text{SNa}\cdot 4\text{H}_2\text{O}$ :

C 50.43, H 6.20, N 8.11

Found: C 50.14, H 6.28, N 8.12

5 Example 14

To a solution of a mixture of starting compound (14) (300 mg), 2-oxo-1,3-diacetoxyp propane (121 mg) and acetic acid (40  $\mu$ l) in a mixture of methanol (4.0 ml) and DMF (4.0 ml) was added sodium cyanoborohydride (29 mg) with stirring at ambient temperature, and the mixture was stirred at the same temperature overnight. The reaction mixture was concentrated in vacuo. To the resulting residue was added pH 6.86 standard buffer solution (10 ml) and acetonitrile (2 ml), and the solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (80 ml) eluting with 40% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (14) (60 mg).

20 NMR (DMSO- $d_6$  +  $D_2O$ ,  $\delta$ ): 0.98 (3H, d,  $J=6.83$ Hz), 1.07 (3H, d,  $J=5.34$ Hz), 1.20-1.60 (10H, m), 1.60-1.90 (5H, m), 1.96 (3H, s), 2.01 (3H, s), 3.20 (3H, s), 3.31 (4H, t,  $J=6.33$ Hz), 3.80-4.55 (16H, m), 4.75-4.90 (2H, m), 6.65-6.80 (2H, m), 7.03 (1H, s), 7.14 (2H, d,  $J=8.84$ Hz), 25 7.90-8.15 (6H, m)

ESI MASS (m/z) (Negative): 1455.3 ( $M^+-1$ )

Example 15

To a solution of starting compound (15) (58 mg) in a mixture of methanol (3 ml) and water (3 ml) were added morpholine (35  $\mu$ l) and saturated aqueous sodium carbonate (1 ml), and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was poured into pH 6.86 standard buffer solution (60 ml), and the solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso

35



Co., Ltd.)) (50 ml) eluting with 30% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (15) (35 mg).

5 NMR (DMSO- $d_6$  +  $D_2O$ ,  $\delta$ ): 0.97 (3H, d,  $J=6.78\text{Hz}$ ), 1.12 (3H, broad s), 1.25-1.65 (8H, m), 1.65-2.00 (4H, m), 2.01 (3H, d, s), 3.21 (3H, s), 3.31 (4H, t,  $J=6.34\text{Hz}$ ), 3.70-4.50 (14H, m), 4.85-4.90 (2H, m), 6.60-6.95 (2H, m), 7.00 (1H, s), 7.14 (2H, d,  $J=8.74\text{Hz}$ ), 8.00 (2H, d,  $J=8.77\text{Hz}$ ), 8.03 (2H, d,  $J=7.63\text{Hz}$ ), 8.12 (2H, d,  $J=8.42\text{Hz}$ )

ESI MASS (m/z) (Negative): 1413.4 ( $M^+-1\text{-Na}$ )

#### Example 16

15 To a solution of starting compound (16) (100 mg) in DMF (3 ml) were added 4-[5-[4-(6-methoxyhexyl)phenyl][1,3,4]-thiadiazol-2-yl]benzoic acid benzotriazol-1-yl ester (71 mg) and diisopropylethylamine (23  $\mu\text{l}$ ) with stirring, and the mixture was stirred at ambient temperature overnight. To the reaction mixture was added ethyl acetate (30 ml). The resulting precipitates were collected by filtration, washed with ethyl acetate (10 ml) and dried in vacuo. The resulting residue was dissolved in a mixture of pH 6.86 standard buffer solution and 1N sodium hydroxide, and insoluble materials were filtered off and the solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (50 ml) eluting with 30% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (16) (86.5 mg).

30 NMR (DMSO- $d_6$  +  $D_2O$ ,  $\delta$ ): 0.97 (3H, d,  $J=6.53\text{Hz}$ ), 1.08 (3H, d,  $J=8.66\text{Hz}$ ), 1.30-2.00 (14H, m), 2.80-3.10 (4H, m), 3.22 (3H, s), 3.90-4.55 (16H, m), 4.65-4.90 (2H, m), 5.10-5.40 (2H, m), 6.82 (2H, br s), 7.00 (1H, s), 7.14 (2H, d,  $J=9.17\text{Hz}$ ), 7.90-8.20 (6H, m)

ESI MASS (m/z) (Negative): 1441.4 ( $M^+-1-Na$ )

Example 17

To a solution of starting compound (17) (200 mg) in  
5 N,N-dimethylformamide (DMF) (3 ml) were added 4'-[4-4-(cis-  
2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]-1,1'-  
biphenyl-4-carboxylic acid benzotriazol-1-yl ester (57 mg) and  
diisopropylethylamine (22  $\mu$ l) with stirring, and the mixture was  
10 stirred at ambient temperature overnight. To the reaction  
mixture was added ethyl acetate (30 ml). The resulting  
precipitates were collected by filtration, washed with ethyl  
acetate (10 ml) and dried in vacuo. The resulting residue was  
dissolved in a mixture of pH 6.86 standard buffer solution and  
15 1N sodium hydroxide, and insoluble material were filtered off  
and the solution was subjected to column chromatography on ODS  
(Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso  
Co., Ltd.)) (100 ml) eluting with 40% acetonitrile in water. The  
fractions containing the object compound were collected and  
evaporated under reduced pressure to remove acetonitrile. The  
20 residue was lyophilized to give object compound (17) (230 mg).

NMR (DMSO- $d_6$  +  $D_2O$ ,  $\delta$ ): 0.97 (3H, d,  $J=6.82$ Hz), 1.14  
(6H, d,  $J=6.16$ Hz), 1.25 (3H, d,  $J=6.34$ Hz), 1.30-2.40  
(6H, m), 3.00-3.40 (10H, m), 3.60-4.10 (10H, m),  
4.10-4.55 (6H, m), 4.60-4.80 (4H, m), 5.05-5.50 (4H,  
25 m), 5.80-6.10 (2H, m), 6.80-7.00 (4H, m), 7.08 (2H,  
d,  $J=8.10$ Hz), 7.11 (2H, d,  $J=8.88$ Hz), 7.42 (1H, s),  
7.66 (2H, d,  $J=8.64$ Hz), 7.72 (2H, d,  $J=8.46$ Hz), 7.93  
(2H, d,  $J=8.38$ Hz)

ESI MASS (m/z) (Negative): 1584.6 ( $M^+-Na$ )

30

Example 18

A mixture of 4-[5-[4-(6-methoxyhexyloxy)phenyl]-  
isoxazol-3-yl]benzoic acid (70 mg), 1-hydroxybenzotriazole  
(35.8 mg), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide  
35 hydrochloride (40.6 mg) and N,N-diisopropylethylamine (46.1  $\mu$ l)

in N,N-dimethylformamide (2 ml) was stirred for 3 hours. To the reaction mixture was added starting compound (18) (200 mg) and the resulting mixture was stirred for 19 hours. To the reaction mixture was added ethyl acetate (100 ml). The resulting precipitate was collected by filtration and washed with diisopropyl ether to give object compound (18) as a crude white powder (294.4 mg), that was used crude in the next reaction.

The following compound was obtained according to a similar manner to that of Example 18.

#### Example 19

The object compound (19) was used directly in the next reaction without purification.

#### Example 20

To a solution of starting compound (20) (287.9 mg) in N,N-dimethylformamide (3 ml) was added piperidine (0.17 ml) at room temperature. The solution was stirred for 1 hour at the same temperature. Ethyl acetate was added to the reaction mixture. The powder was collected by filtration to give crude material (203.8 mg). The crude material was purified by column chromatography on ODS to give object compound (20) (85.6 mg).

IR (KBr): 1632, 1512, 1446, 1230  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.97 (3H, d,  $J=6.7\text{Hz}$ ), 1.08 (3H, d,  $J=5.2\text{Hz}$ ), 1.5-3.0 (23H, m), 3.0-4.5 (39H, m), 4.6-5.4 (10H, m), 6.6-7.1 (11H, m), 7.17 (2H, d,  $J=8.7\text{Hz}$ ), 7.3-7.6 (2H, m), 7.81 (2H, d,  $J=8.6\text{Hz}$ ), 8.0-8.5 (2H, m), 8.71 (1H, s)

MASS (m/z): 1488 ( $M^+ + 1$ )

The following compound was obtained according to a similar manner to that of Example 20.

#### Example 21

IR (KBr): 1632, 1512, 1444, 1232  $\text{cm}^{-1}$

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 0.97 (3H, d,  $J=6.8\text{Hz}$ ), 1.08 (3H, d,  $J=5.5\text{Hz}$ ), 1.2-3.0 (28H, m), 3.0-4.5 (38H, m), 4.6-5.4 (10H, m), 6.6-7.1 (9H, m), 7.3-7.7 (2H, m), 7.7-8.0 (3H, m), 8.0-8.5 (5H, m), 8.71 (1H, s)

MASS ( $m/z$ ): 1456 ( $M^+-1$ )

### Example 22

To a solution of starting compound (22) (0.22 g) in a mixture of methanol (4 ml) and THF (1 ml) were successively added triphenylphosphine (14 mg), tetrakis(triphenylphosphine)palladium(0) (8 mg) and morpholine (40  $\mu\text{l}$ ) with stirring and the mixture was stirred at ambient temperature for 3 hours. The reaction mixture was concentrated in vacuo. The resulting residue was dissolved in a mixture of pH 6.86 standard buffer solution and 1N sodium hydroxide, insoluble materials were filtered off and the solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (100 ml) eluting with 30% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (22) (85 mg).

IR (KBr): 1633, 1537, 1516, 1450, 1234  $\text{cm}^{-1}$

NMR ( $\text{DMSO}-d_6 + \text{D}_2\text{O}$ ,  $\delta$ ): 0.98 (3H, d,  $J=7.09\text{Hz}$ ), 1.05 (3H, d,  $J=7.00\text{Hz}$ ), 1.15 (6H, d,  $J=6.21\text{Hz}$ ), 1.60-2.30 (8H, m), 2.75-3.45 (14H, m), 3.80-4.50 (10H, m), 4.81 (1H, br s), 6.65-7.20 (8H, m), 7.50-7.80 (5H, m), 7.94 (2H, d,  $J=8.49\text{Hz}$ )

ESI MASS ( $m/z$ ) (Negative): 1416.4 ( $M^++1$ )

Elemental Analysis Calcd. for  $\text{C}_{67}\text{H}_{91}\text{N}_{11}\text{O}_{21}\text{S}\cdot 7\text{H}_2\text{O}$ :

C 52.10, H 6.85, N 9.97

Found: C 52.29, H 6.60, N 9.61

The following compounds [Examples 23 to 32] were obtained

according to a similar manner to that of Example 22.

Example 23

5 NMR (DMSO- $d_6$  +  $D_2O$ ,  $\delta$ ): 0.97 (3H, d,  $J=6.84\text{Hz}$ ), 1.11 (3H, d,  $J=5.43\text{Hz}$ ), 1.30-1.90 (14H, m), 2.80-3.20 (5H, m), 3.22 (3H, s), 3.31 (2H, t,  $J=6.16\text{Hz}$ ), 3.80-4.20 (6H, m), 4.26 (2H, broad s), 4.30-4.50 (3H, m), 4.70-4.90 (1H, m), 6.72 (1H, d,  $J=8.14\text{Hz}$ ), 6.78 (1H, d,  $J=10.5\text{Hz}$ ), 7.01 (1H, s), 7.14 (2H, d,  $J=8.70\text{Hz}$ ), 7.98 (2H, d,  $J=8.90\text{Hz}$ ), 8.05 (2H, d,  $J=8.68\text{Hz}$ ), 8.12 (2H, d,  $J=8.68\text{Hz}$ )

10 MASS (m/z) (Negative): 1357.5 ( $M^{+1}$ )

Example 24

15 IR (KBr): 2933, 1633, 1531, 1518, 1444, 1419, 1385, 1346  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.90 (3H, d,  $J=6.7\text{Hz}$ ), 0.98 (3H, d,  $J=6.7\text{Hz}$ ), 1.12 (3H, d,  $J=5.5\text{Hz}$ ), 1.32-2.68 (23H, m), 2.82-2.98 (2H, m), 3.07-4.54 (25H, m), 4.74-5.50 (10H, m), 6.70 (1H, d,  $J=8.1\text{Hz}$ ), 6.78 (1H, d,  $J=8.1\text{Hz}$ ), 7.00 (1H, s), 7.09 (2H, d,  $J=9.0\text{Hz}$ ), 7.36-7.70 (2H, m), 7.86 (2H, d,  $J=8.8\text{Hz}$ ), 8.00-8.50 (6H, m), 8.71 (1H, s), 8.82-8.97 (1H, m)

20 ESI MASS (m/z): 1407.5 ( $M^{+1}$ )

25 Elemental Analysis Calcd. for  $C_{64}H_{88}N_{12}O_{20}S_2 \cdot 7H_2O$ :  
C 50.06, H 6.69, N 10.94  
Found: C 49.99, H 6.76, N 10.73

Example 25

30 IR (KBr): 3353.6, 1666.2, 1648.8, 1631.5, 1540.8, 1508.1, 1452.1, 1436.7, 1257.4  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.98 (3H, d,  $J=6.7\text{Hz}$ ), 1.11 (3H, d,  $J=5.5\text{Hz}$ ), 1.2-5.6 (59H, m), 6.71 (1H, d,  $J=8.2\text{Hz}$ ), 6.78 (1H, d,  $J=9.6\text{Hz}$ ), 7.00 (1H, s), 7.12 (2H, d,  $J=8.8\text{Hz}$ ), 7.44 (1H, d,  $J=8.5\text{Hz}$ ), 7.55 (1H, s), 7.85

35

(2H, d, J=8.6Hz), 7.99 (2H, d, J=8.5Hz), 8.05 (2H, d, J=8.6Hz), 7.3-8.5 (3H, m), 8.71 (1H, s), 8.7-9.0 (1H, m)

MASS (m/z): 1340.4 ( $M^-Na$ )

5 Elemental Analysis Calcd. for  $C_{61}H_{83}N_9O_{23}S \cdot 6H_2O$ :  
C 50.51, H 6.60, N 8.69  
Found: C 50.67, H 6.60, N 8.62

#### Example 26

10 IR (KBr): 3380.6, 1675.8, 1648.8, 1621.8, 1540.8,  
1506.1, 1454.1, 1434.8, 1257.4  $cm^{-1}$   
NMR (DMSO- $d_6$ ,  $\delta$ ): 0.98 (3H, d, J=6.8Hz), 1.03 (6H, d, J=6.3Hz), 1.12 (3H, d, J=5.5Hz), 1.2-5.6 (64H, m),  
6.71 (1H, d, J=8.1Hz), 6.77 (1H, d, J=9.4Hz), 7.00 (1H, s),  
15 7.12 (2H, d, J=8.9Hz), 7.43 (1H, d, J=7.7Hz), 7.55 (1H, s), 7.85 (2H, d, J=8.6Hz), 7.99 (2H, d, J=8.8Hz), 8.05 (2H, d, J=8.8Hz), 7.3-8.5 (3H, m), 8.71 (1H, s), 8.82 (1H, d, J=5.7Hz)  
MASS (m/z): 1437.4 ( $M^-1$ )  
20 Elemental Analysis Calcd. for  $C_{67}H_{94}N_{10}O_{23}S \cdot 6H_2O$ :  
C 52.00, H 6.90, N 9.05  
Found: C 51.91, H 6.91, N 8.77

#### Example 27

25 IR (KBr): 2931, 2854, 1632, 1510, 1446, 1385, 1325  $cm^{-1}$   
NMR (DMSO- $d_6$ ,  $\delta$ ): 0.97 (3H, d, J=6.7Hz), 1.12 (3H, d, J=5.5Hz), 1.08-2.62 (23H, m), 2.62-4.50 (37H, m), 4.66-5.45 (10H, m), 6.70 (1H, d, J=8.1Hz), 6.78 (1H, d, J=8.1Hz), 6.83-7.09 (7H, m), 7.34-8.00 (3H, m),  
30 7.80 (2H, d, J=8.7Hz), 8.00-8.49 (2H, m), 8.71 (1H, s)  
MASS (m/z): 1408.4 ( $M^+1$ )  
Elemental Analysis Calcd. for  $C_{66}H_{95}N_{11}O_{21}S \cdot 7H_2O$ :  
C 51.59, H 7.15, N 10.03  
35 Found: C 51.77, H 7.05, N 9.82

Example 28

IR (KBr): 2974, 2937, 1633, 1533, 1512, 1444, 1383,  
1327  $\text{cm}^{-1}$

5 NMR (DMSO- $d_6$ ,  $\delta$ ): 0.98 (3H, d,  $J=6.7\text{Hz}$ ), 1.11 (3H, d,  
 $J=5.2\text{Hz}$ ), 1.18 (6H, d,  $J=6.1\text{Hz}$ ), 1.59-2.65 (11H, m),  
2.65-4.56 (27H, m), 4.70-5.36 (10H, m), 6.71 (1H, d,  
 $J=8.1\text{Hz}$ ), 6.78 (1H, d,  $J=8.1\text{Hz}$ ), 7.00 (1H, s), 7.08  
10 (2H, d,  $J=8.8\text{Hz}$ ), 7.38-7.99 (3H, m), 7.68 (2H, d,  
 $J=8.7\text{Hz}$ ), 7.86 (2H, d,  $J=8.5\text{Hz}$ ), 8.00-8.46 (7H, m),  
8.71 (1H, s), 8.80-8.95 (1H, m)

MASS (m/z): 1440.3 ( $\text{M}^+ + \text{Na}$ )

Elemental Analysis Calcd. for  $\text{C}_{65}\text{H}_{85}\text{N}_{11}\text{O}_{21}\text{S}_2\cdot 8\text{H}_2\text{O}$ :

C 49.96, H 6.39, N 9.86

15 Found: C 50.03, H 6.17, N 9.47

Example 29

IR (KBr): 3386.4, 1633.4, 1502.3, 1446.4, 1232.3  $\text{cm}^{-1}$

20 NMR (DMSO- $d_6$ ,  $\delta$ ): 0.96 (3H, d,  $J=6.6\text{Hz}$ ), 1.0-1.3 (9H,  
m), 1.3-5.6 (57H, m), 6.70 (1H, d,  $J=8.1\text{Hz}$ ), 6.77 (1H,  
d,  $J=9.7\text{Hz}$ ), 6.9-7.2 (7H, m), 7.3-9.0 (13H, m).

MASS (m/z): 1416.4 ( $\text{M}^- - \text{Na}$ )

Example 30

25 IR (KBr): 3365.2, 1631.5, 1517.7, 1465.6, 1444.4,  
1257.4  $\text{cm}^{-1}$

MASS (m/z): 1368.3 ( $\text{M}^- - 1$ )

Elemental Analysis Calcd. for  $\text{C}_{60}\text{H}_{79}\text{N}_{11}\text{O}_{22}\text{S}_2\cdot 7\text{H}_2\text{O}$ :

C 48.15, H 6.26, N 10.30

30 Found: C 48.26, H 6.17, N 10.35

Example 31

IR (KBr): 3458, 3425, 3398, 3386, 3363, 2935, 1635,  
1523, 1462, 1244  $\text{cm}^{-1}$

35 NMR (DMSO- $d_6$ ,  $\delta$ ): 0.98 (3H, d,  $J=6.7\text{Hz}$ ), 1.12 (3H, d,

J=5.6Hz), 1.20-1.60 (12H, m), 1.70-2.45 (12H, m),  
 2.80-3.20 (9H, m), 3.21 (3H, s), 3.40-4.60 (24H, m),  
 4.70-5.40 (12H, m), 6.71 (1H, d, J=8.1Hz), 6.60-6.80  
 (1H, m), 7.00 (1H, d, J=1.4Hz), 7.08 (2H, d, J=9Hz),  
 7.35-7.65 (2H, m), 7.75 (2H, d, J=8.8Hz), 7.80-8.10  
 (5H, m), 8.20-8.40 (1H, m), 8.60-8.80 (2H, m), 8.80  
 (1H, s)

MASS (m/z) (API-ES-Negative): 1497 ( $M^+ - 1 + Na$ )

Elemental Analysis Calcd. for  $C_{67}H_{91}N_{12}O_{21}S_3 \cdot 8-1/2H_2O$ :

C 48.75, M 6.55, N 10.18

Found: C 48.52, H 6.47, N 9.74

### Example 32

IR (KBr): 3464, 3425, 3398, 3386, 3363, 2940, 1635,  
 1523, 1461  $cm^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.97 (3H, d, J=6.8Hz), 1.12 (3H, d,  
 J=5.6Hz), 1.40-1.60 (6H, m), 1.65-2.45 (9H, m),  
 2.60-3.20 (6H, m), 3.21 (3H, s), 3.40-3.80 (15H, m),  
 3.80-4.60 (14H, m), 4.65-5.50 (9H, m), 6.71 (1H, d,  
 J=8.1Hz), 6.75 (1H, dd, J=1.6 and 8.3Hz), 7.03 (1H,  
 d, J=1.6Hz), 7.09 (2H, d, J=9Hz), 7.40-7.65 (2H, m),  
 7.75 (2H, d, J=8.8Hz), 7.80-8.00 (4H, m), 8.18-8.30  
 (1H, m), 8.55-8.70 (1H, m), 8.75 (2H, d, J=8.7Hz)

MASS (m/z) (API-ES-Negative): 1453 ( $M^+$ )

Elemental Analysis Calcd. for  $C_{65}H_{88}N_{12}O_{22}S_2 \cdot 6H_2O$ :

C 49.27, H 6.25, N 10.61

Found: C 49.03, H 6.33, N 10.30

### Example 33

To a solution of starting compound (33) (12.50 g) and  
 diisopropylethylamine (3.67 ml) in N,N-dimethylformamide (250  
 ml) was added 4-[2-[4-(4-methoxybutoxy)phenyl]imidazo-  
 [2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid benzotriazol-1-yl  
 ester at room temperature. The solution was stirred for 4 hours  
 at the same temperature, during which period additional 4-



[2-[4-(4-methoxybutoxy)phenyl]imidazo[2,1-b][1,3,4]-thiadiazol-6-yl]benzoic acid benzotriazol-1-yl ester was added to the mixture. The reaction mixture was then filtered. To the filtrate was added piperidine (9.33 ml) at room temperature. The solution was stirred for 1 hour at the same temperature. Ethyl acetate was added to the reaction mixture. The powder was collected by filtration to give crude material (16.12 g). The crude material was purified by column chromatography on ODS to give object compound (33) (11.10 g).

10 IR (KBr): 1659, 1633, 1529, 1518, 1466, 1444, 1255  $\text{cm}^{-1}$   
NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 0.98 (3H, d,  $J=6.7\text{Hz}$ ), 1.00 (3H, d,  $J=5.8\text{Hz}$ ), 1.5-2.6 (12H, m), 2.8-3.6 (33H, m), 4.7-5.4 (10H, m), 6.65-6.85 (2H, m), 7.00 (1H, s), 7.15 (2H, d,  $J=8.9\text{Hz}$ ), 7.3-7.7 (2H, m), 7.90 (2H, d,  $J=8.8\text{Hz}$ ), 7.96 (4H, s), 8.0-8.5 (2H, m), 8.71 (1H, s),  
15 8.85 (1H, s)  
MASS ( $m/z$ ): 1392 ( $M^+ + 23$ )  
Elemental Analysis Calcd. for  $\text{C}_{60}\text{H}_{79}\text{N}_{11}\text{O}_{22}\text{S}_2 \cdot 5\text{H}_2\text{O}$ :  
C 49.34, H 6.14, N 10.55  
20 Found: C 49.30, H 6.23, N 10.53

The following compounds [Examples 34 and 44] were obtained according to a similar manner to that of Example 33.

25 Example 34

IR (KBr): 3463, 3423, 3359, 2941, 2883, 1633, 1614, 1523, 1462  $\text{cm}^{-1}$   
NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 0.98 (3H, d,  $J=6.7\text{Hz}$ ), 1.10 (3H, d,  $J=5.6\text{Hz}$ ), 1.35-2.20 (10H, m), 2.80-3.20 (2H, m), 3.22 (3H, s), 3.30-3.80 (10H, m), 3.80-4.60 (10H, m), 4.70-5.35 (9H, m), 6.71 (1H, d,  $J=8.1\text{Hz}$ ), 6.65-6.90 (1H, m), 7.00 (1H, br s), 7.09 (2H, d,  $J=9\text{Hz}$ ), 7.40-7.70 (2H, m), 7.43 (2H, d,  $J=8.6\text{Hz}$ ), 7.80-8.00 (4H, m), 8.10-8.50 (2H, m), 8.60-8.80 (3H, m)  
30  
35 MASS ( $m/z$ ) (API-ES-Negative): 1440 ( $M^+ - 1$ )

Elemental Analysis Calcd. for  $C_{64}H_{86}N_{12}O_{22}S_2 \cdot 6-1/2H_2O$ :

C 49.36, H 6.36, N 10.80

Found: C 49.20, H 6.50, N 10.66

5 Example 35

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.90 (3H, d,  $J=6.7\text{Hz}$ ), 0.98 (3H, d,  $J=6.8\text{Hz}$ ), 1.11 (3H, d,  $J=5.7\text{Hz}$ ), 1.43-5.24 (62H, m), 6.69-8.85 (17H, m)

MASS (m/z): 1408.5

10

Example 36

MASS (m/z): 1491.4 ( $M^+-HN^+Et(iPr)_2$ )

Example 37

15 MASS (m/z): 1576.5 ( $M^+-HN^+Et(iPr)_2$ )

Example 38

MASS (m/z): 1584.4 ( $M^+-HN^+Et(iPr)_2$ )

20 Example 39

The object compound (39) was used directly in the next reaction without purification.

Example 40

25 The object compound (40) was used directly in the next reaction without purification.

Example 41

30 The object compound (41) was used directly in the next reaction without purification.

Example 42

The object compound (42) was used directly in the next reaction without purification.

35

The following compounds [Examples 43 and 44] were obtained according to a similar manner to that of Example 20.

Example 43

- 5 NMR (DMSO- $d_6$  +  $D_2O$ ,  $\delta$ ): 0.89 (3H, d,  $J=6.22\text{Hz}$ ), 1.14 (3H, br s), 1.35-2.40 (6H, m), 2.65-3.00 (1H, m), 3.60-4.50 (14H, m), 4.55-4.80 (2H, m), 5.28 (1H, s), 6.65-6.80 (2H, m), 6.98 (1H, s), 7.20-7.50 (4H, m), 7.69 (2H, d,  $J=7.08\text{Hz}$ ), 7.84 (2H, d,  $J=7.27\text{Hz}$ )
- 10 ESI MASS (m/z) (Negative): 1185.4 ( $M^+-1$ )

Example 44

- 15 NMR (DMSO- $d_6$  +  $D_2O$ ,  $\delta$ ): 0.95 (3H, d,  $J=6.77\text{Hz}$ ), 1.12 (3H, d,  $J=4.94\text{Hz}$ ), 1.20-1.75 (4H, m), 1.80-2.50 (4H, m), 2.65-2.90 (1H, m), 3.00-3.40 (4H, m), 3.60-4.05 (6H, m), 4.17 (2H,  $J=7.17\text{Hz}$ ), 4.25-4.90 (7H, m), 5.05-5.35 (2H, m), 5.75-6.10 (1H, m), 6.65-6.85 (2H, m), 6.97 (1H, s)
- 20 ESI MASS (m/z) (Positive): 1048.3 ( $M^+$ )

Example 45

- To a solution of a mixture of starting compound (45) (2.0 g), 1,3-dihydroxyacetone (364 mg) and acetic acid (0.58 ml) in a mixture of methanol (30 ml) and DMF (14 ml) was added sodium cyanoborohydride (258 mg) with stirring at ambient temperature, and the mixture was stirred at the same temperature overnight. To the reaction mixture was added ethyl acetate (200 ml). The resulting precipitates were collected by filtration and dried in vacuo. The precipitates were dissolved in a mixture of pH 6.86 standard buffer solution (100 ml) and acetonitrile (20 ml), and the solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (200 ml) eluting with 15% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The
- 35

residue was lyophilized to give object compound (45) (1.63 g).

NMR (DMSO- $d_6$  +  $D_2O$ ,  $\delta$ ): 0.98 (3H, d,  $J=6.75\text{Hz}$ ), 1.08  
(3H, d,  $J=5.69\text{Hz}$ ), 1.35 (9H, s), 1.45-2.05 (5H, m),  
2.15-2.50 (4H, m), 2.70-3.35 (7H, m), 3.50-4.50 (16H,  
5 m), 4.70-4.90 (2H, m), 6.71 (1H, d,  $J=8.13\text{Hz}$ ), 6.78  
(1H, d,  $J=9.91\text{Hz}$ ), 7.01 (1H, s)  
ESI MASS (m/z) (Positive): 1088.4 ( $M^+Na$ )

The following compounds [Examples 46 to 52] were obtained  
10 according to a similar manner to that of Example 45.

Example 46

IR (KBr): 3353.6, 1635.3, 1444.4, 1257.4, 1085.7,  
1047.2  $\text{cm}^{-1}$

15 NMR (DMSO- $d_6$ ,  $\delta$ ): 0.97 (3H, d,  $J=6.6\text{Hz}$ ), 1.14 (3H, d,  
 $J=5.4\text{Hz}$ ), 1.2-5.6 (61H, m), 6.71 (1H, d,  $J=8.0\text{Hz}$ ),  
6.77 (1H, d,  $J=10.3\text{Hz}$ ), 6.96 (1H, s), 7.13 (2H, d,  
 $J=8.8\text{Hz}$ ), 7.97 (2H, d,  $J=8.7\text{Hz}$ ), 8.08 (4H, s), 7.4-8.9  
(6H, m)

20 MASS (m/z): 1371.4 ( $M^-1$ )

Example 47

IR (KBr): 3353.6, 1635.3, 1531.2, 1517.7, 1444.4,  
1257.4, 1087.7, 1045.2  $\text{cm}^{-1}$

25 NMR (DMSO- $d_6$ ,  $\delta$ ): 0.97 (3H, d,  $J=6.7\text{Hz}$ ), 1.0-5.6 (64H,  
m), 6.6-6.8 (2H, m), 6.99 (1H, s), 7.14 (2H, d,  
 $J=8.9\text{Hz}$ ), 7.97 (2H, d,  $J=8.8\text{Hz}$ ), 8.08 (4H, s), 7.3-9.0  
(6H, m)

MASS (m/z): 1371.3 ( $M^-1$ )

30 Elemental Analysis Calcd. for  $C_{61}H_{84}N_{10}O_{22}S_2 \cdot 7H_2O$ :

C 48.86, H 6.59, N 9.34

Found: C 49.00, H 6.39, N 9.24

Example 48

35 IR (KBr): 3384.5, 1658.5, 1635.3, 1529.3, 1517.7,

1446.4, 1257.4, 1085.7, 1045.2  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.97 (3H, d,  $J=6.7\text{Hz}$ ), 1.13 (3H, d,  $J=5.5\text{Hz}$ ), 1.2-5.3 (65H, m), 6.91 (1H, d,  $J=8.1\text{Hz}$ ), 6.77 (1H, d,  $J=9.9\text{Hz}$ ), 6.97 (1H, s), 7.13 (2H, d,  $J=8.9\text{Hz}$ ), 7.97 (2H, d,  $J=8.8\text{Hz}$ ), 8.09 (4H, s), 7.4-8.9 (6H, m)

MASS (m/z): 1431.3 ( $M^{-1}$ )

Elemental Analysis Calcd. for  $\text{C}_{63}\text{H}_{86}\text{N}_{10}\text{O}_{24}\text{S}_2\cdot 8\text{H}_2\text{O}$ :

C 47.96, H 6.64, N 8.88

Found: C 48.21, H 6.35, N 8.87

#### Example 49

IR (KBr): 3371.0, 1648.8, 1631.5, 1538.9, 1513.8, 1442.5, 1257.4, 1083.8, 1045.2  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.97 (3H, d,  $J=6.7\text{Hz}$ ), 1.10 (3H, d,  $J=5.5\text{Hz}$ ), 1.2-5.4 (65H, m), 6.71 (1H, d,  $J=8.2\text{Hz}$ ), 6.77 (1H, d,  $J=10.2\text{Hz}$ ), 6.99 (1H, s), 7.14 (2H, d,  $J=8.7\text{Hz}$ ), 7.97 (2H, d,  $J=8.7\text{Hz}$ ), 8.09 (4H, s), 7.3-9.0 (6H, m)

MASS (m/z): 1401.3 ( $M^{-1}$ )

Elemental Analysis Calcd. for  $\text{C}_{62}\text{H}_{86}\text{N}_{10}\text{O}_{23}\text{S}_2\cdot 7\text{H}_2\text{O}$ :

C 48.68, H 6.59, N 9.16

Found: C 48.83, H 6.39, N 9.13

#### Example 50

IR (KBr): 3350, 2933, 2862, 1658.5, 1635, 1516, 1444, 1257, 1084, 1043  $\text{cm}^{-1}$

NMR (DMSO- $d_6$  +  $\text{D}_2\text{O}$ ,  $\delta$ ): 0.98 (3H, d,  $J=6.7\text{Hz}$ ), 1.09 (3H, d,  $J=5.8\text{Hz}$ ), 1.2-4.8 (49H, complex m), 3.21 (3H, s), 3.31 (2H, t,  $J=6.4\text{Hz}$ ), 6.8-6.9 (2H, m), 7.02 (1H, br s), 7.15 (2H, d,  $J=8.9\text{Hz}$ ), 7.98 (2H, d,  $J=8.9\text{Hz}$ ), 8.10 (4H, s)

MASS (m/z): 1485.4 ( $M^+ + \text{Na}$ )

Elemental Analysis Calcd. for  $\text{C}_{64}\text{H}_{90}\text{N}_{10}\text{O}_{25}\text{S}_2\cdot 6\text{H}_2\text{O}$ :

C 48.91, H 6.54, N 8.91

Found: C 49.18, H 6.55, N 8.90

Example 51

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.86 (3H, d,  $J=6.3\text{Hz}$ ), 0.98 (3H, d,  
5  $J=6.8\text{Hz}$ ), 1.11 (3H, d,  $J=5.7\text{Hz}$ ), 1.21-5.24 (62H, m),  
6.69-8.89 (17H, m)  
MASS (m/z): 1408.5, 1407.4 ( $M^+-1$ )  
Elemental Analysis Calcd. for  $C_{64}H_{88}N_{12}O_{20}S_2 \cdot 7H_2O$ :  
C 50.06, H 6.69, N 10.94  
10 Found: C 49.96, H 6.86, N 10.82

Example 52

IR (KBr): 1633, 1606, 1529, 1518, 1466  $\text{cm}^{-1}$   
NMR (DMSO- $d_6$ ,  $\delta$ ): 0.96 (3H, d,  $J=6.7\text{Hz}$ ), 1.11 (3H, d,  
15  $J=5.7\text{Hz}$ ), 1.2-2.6 (18H, m), 2.8-4.6 (39H, m), 4.7-  
5.4 (9H, m), 6.7-6.9 (2H, m), 7.0-7.2 (3H, m), 7.3-7.6  
(2H, m), 7.75 (2H, d,  $J=8.7\text{Hz}$ ), 7.7-8.0 (5H, m),  
8.2-8.5 (1H, m), 8.6-8.75 (1H, m), 8.80 (1H, s), 8.85  
(1H, s)  
20 MASS (m/z): 1481 ( $M^+-1$ )  
Elemental Analysis Calcd. for  $C_{66}H_{90}N_{12}O_{23}S_2 \cdot 7H_2O$ :  
C 49.25, H 6.51, N 10.44  
Found: C 49.30, H 6.34, N 10.40

25 The following compound was obtained according to a similar  
manner to that of Example 1.

Example 53

IR (KBr): 2937.1, 1651, 1631.5, 1539, 1523.5  $\text{cm}^{-1}$   
30 MASS (m/z): 1293.3 ( $M^++1$ )

Example 54

To a solution of starting compound (54) (300 mg) in methanol  
(12 ml) was added 10% hydrochloric acid in methanol (6 ml) at  
35 room temperature. The solution was stirred for 3 hours at the

same temperature. The solvent was evaporated under reduced pressure to remove hydrochloric acid and methanol. To the residue was added water and the mixture was lyophilized. The residue was purified by column chromatography on ODS to give

5 object compound (54) (119 mg).

IR (KBr): 1649, 1633, 1608, 1539, 1525  $\text{cm}^{-1}$

MASS (m/z): 1351 ( $\text{M}^+ + 23$ )

Elemental Analysis Calcd. for  $\text{C}_{64}\text{H}_{88}\text{N}_{12}\text{O}_{17}\text{S}\cdot 8\text{H}_2\text{O}$ :

C 52.16, H 7.11, N 11.41

10 Found: C 52.13, H 7.05, N 11.36

The following compounds [Example 55 to 71] were obtained according to a similar manner to that of Example 33.

15 Example 55

IR (KBr): 3358, 1633, 1608, 1535, 1516, 1443, 1419, 1271, 1238  $\text{cm}^{-1}$

20 NMR ( $\text{DMSO}-d_6 + \text{D}_2\text{O}$ ,  $\delta$ ): 0.89 (6H, s), 0.98 (3H, d,  $J=6.7\text{Hz}$ ), 1.10 (3H, d,  $J=5.8\text{Hz}$ ), 1.1-2.6 (20H, m), 2.6-4.5 (29H, m), 4.7-4.9 (2H, m), 6.7-6.9 (2H, m), 7.0-7.1 (1H, m), 7.08 (2H, d,  $J=9.2\text{Hz}$ ), 7.86 (2H, d,  $J=8.5\text{Hz}$ ), 8.0-8.2 (4H, m)

ESI MASS (m/z) (Negative): 1422.3 ( $\text{M}^- - 1$ )

Elemental Analysis Calcd. for  $\text{C}_{65}\text{H}_{90}\text{N}_{12}\text{O}_{20}\text{S}_2\cdot 7.5\text{H}_2\text{O}$ :

25 C 50.09, H 6.79, N 10.78

Found: C 49.94, H 6.59, N 10.52

Example 56

30 IR (KBr): 3462, 3458, 3425, 3399, 3367, 1633, 1578, 1440  $\text{cm}^{-1}$

35 NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 0.98 (3H, d,  $J=6.7\text{Hz}$ ), 1.11 (3H, d,  $J=5.6\text{Hz}$ ), 1.20-1.50 (3H, m), 1.60-2.40 (18H, m), 2.50-2.70 (4H, m), 2.75-3.20 (7H, m), 3.40-3.60 (6H, m), 3.70-4.50 (14H, m), 4.62 (2H, br s), 4.65-4.80 (3H, m), 4.80-5.40 (8H, m), 6.60-6.80 (2H, m), 7.00 (1H,

br s), 7.07 (2H, d, J=8.9Hz), 7.40-7.60 (2H, m), 7.85  
(2H, d, J=8.7Hz), 7.90-8.20 (4H, m), 8.20-8.40 (1H,  
m), 8.71 (1H, s), 8.85 (1H, d, J=6.9Hz)

API-ES MASS (m/z) (Negative): 1408 ( $M^+ + 1$ )

5 Elemental Analysis Calcd. for  $C_{64}H_{86}N_{12}O_{20}S_2 \cdot 7H_2O$ :

C 50.10, H 6.52, N 10.96

Found: C 50.29, M 6.48, N 10.77

#### Example 57

10 IR (KBr): 1666, 1649, 1632, 1554, 1541, 1514, 1450, 1443,  
1419, 1240  $cm^{-1}$

NMR (DMSO- $d_6 + D_2O$ ,  $\delta$ ): 0.7-1.3 (17H, m), 1.3-2.6 (7H, m),  
2.7-4.5 (35H, m), 4.7-4.9 (2H, m), 6.7-6.9 (2H, m),  
7.0-7.2 (3H, m), 7.87 (2H, d, J=8.6Hz), 8.0-8.2 (4H,  
15 m)

ESI MASS (m/z) (Positive): 1453.4 ( $M + 2Na$ ) $^{2+}$

Elemental Analysis Calcd. for  $C_{64}H_{88}N_{12}O_{20}S_2 \cdot 6H_2O$ :

C 50.65, H 6.64, N 11.07

Found: C 50.28, H 6.61, N 10.80

20

#### Example 58

Major compound:

ESI MASS (m/z) (Negative): 1538.6 ( $M^- - 1$ )

25

Minor compound:

IR (KBr): 3352, 1659, 1635, 1606, 1529, 1444, 1417, 1274,  
1238  $cm^{-1}$

ESI MASS (m/z) (Negative): 1338.6 ( $M^- - 1$ )

Elemental Analysis Calcd. for  $C_{71}H_{102}N_{12}O_{22}S_2 \cdot 7H_2O$ :

30

C 51.19, H 7.02, N 10.09

Found: C 51.19, H 6.95, N 9.73

#### Example 59

Major compound:

35

ESI MASS (m/z) (Positive): 1598.3 ( $M + 2Na$ ) $^{2+}$



Minor compound:

ESI MASS (m/z) (Negative): 1551.6 (M-2H)<sup>2-</sup>

5 Example 60

IR (KBr): 1664, 1635, 1605, 1446, 1410, 1350, 1329,  
1281 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, D<sub>2</sub>O, δ): 0.98 (3H, d, J=6.7Hz), 1.10 (3H, d,  
J=5.9Hz), 1.1-2.6 (21H, m), 2.8-4.5 (31H, m), 4.7-  
10 4.9 (2H, m), 6.7-6.9 (2H, m), 7.0-7.2 (3H, m), 7.85  
(2H, d, J=8.9Hz), 8.0-8.2 (4H, m)

ESI MASS (m/z) (Negative): 1409.4 (M<sup>-1</sup>)

Elemental Analysis Calcd. for C<sub>64</sub>H<sub>87</sub>N<sub>11</sub>O<sub>21</sub>S<sub>2</sub>·6H<sub>2</sub>O:

C 50.62, H 6.57, N 10.15

15 Found: C 50.40, H 6.61, N 9.92

Example 61

IR (KBr): 2937, 1676, 1651, 1556, 1541, 1514, 1452, 1441,  
1419 cm<sup>-1</sup>

20 NMR (DMSO-d<sub>6</sub>+D<sub>2</sub>O, δ): 0.98 (3H, d, J=6.8Hz), 1.10 (3H, d,  
J=5.7Hz), 1.2-2.6 (17H, m), 2.8-4.5 (37H, m), 4.7-  
4.9 (2H, m), 6.7-6.9 (2H, m), 7.0-7.2 (3H, m), 7.85  
(2H, d, J=8.6Hz), 8.0-8.2 (4H, m)

ESI MASS (m/z) (Negative): 1427.5 (M<sup>-1</sup>)

25 Elemental Analysis Calcd. for C<sub>64</sub>H<sub>89</sub>N<sub>11</sub>O<sub>22</sub>S<sub>2</sub>·5.5H<sub>2</sub>O:

C 50.32, H 6.60, N 10.09

Found: C 50.31, H 6.72, N 10.04

Example 62

30 IR (KBr): 1633, 1606, 1529, 1518, 1444, 1419, 1279,  
1252 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>+D<sub>2</sub>O, δ): 0.98 (3H, d, J=6.7Hz), 1.10 (3H, d,  
J=5.8Hz), 1.2-2.6 (19H, m), 2.8-4.6 (37H, m), 4.7-  
4.9 (2H, m), 6.7-6.9 (2H, m), 7.0-7.2 (3H, m), 7.85  
35 (2H, d, J=8.8Hz), 8.0-8.2 (4H, m)

ESI MASS (m/z) (Negative): 1441.5 ( $M^{-1}$ )

Elemental Analysis Calcd. for  $C_{65}H_{91}N_{11}O_{22}S_2 \cdot 7H_2O$ :

C 49.77, H 6.75, N 9.82

Found: C 49.80, H 6.68, N 9.80

5

Example 63

IR (KBr): 2935, 1633, 1606, 1529, 1518, 1444, 1419, 1273,  
1232  $cm^{-1}$

10 NMR (DMSO- $d_6$ + $D_2O$ ,  $\delta$ ): 0.98 (3H, d,  $J=6.8Hz$ ), 1.10 (3H, d,  
 $J=6.3Hz$ ), 1.2-2.6 (16H, m), 2.7-4.5 (38H, m), 4.7-  
4.9 (2H, m), 6.7-6.9 (2H, m), 7.0-7.2 (3H, m), 7.85  
(2H, d,  $J=7.8Hz$ ), 8.0-8.2 (4H, m)

ESI MASS (m/z) (Negative): 1427.4 ( $M^{-1}$ )

Elemental Analysis Calcd. for  $C_{64}H_{89}N_{11}O_{22}S_2 \cdot 6H_2O$ :

15 C 50.02, H 6.62, N 10.03

Found: C 49.99, H 6.73, N 9.67

Example 64

IR (KBr): 1659, 1633, 1605, 1547, 1529, 1518, 1444,  
1419  $cm^{-1}$

20 NMR (DMSO- $d_6$ + $D_2O$ ,  $\delta$ ): 0.98 (3H, d,  $J=6.8Hz$ ), 1.11 (3H, d,  
 $J=5.7Hz$ ), 1.2-2.6 (18H, m), 2.8-4.5 (38H, m), 4.7-  
4.9 (2H, m), 6.7-6.9 (2H, m), 7.0-7.2 (3H, m), 7.84  
(2H, d,  $J=8.7Hz$ ), 8.0-8.2 (4H, m)

ESI MASS (m/z) (Negative): 1441.5 ( $M^{-1}$ )

25 Elemental Analysis Calcd. for  $C_{65}H_{91}N_{11}O_{22}S_2 \cdot 6H_2O$ :

C 50.34, H 6.69, N 9.94

Found: C 50.12, H 6.78, N 9.87

Example 65

30 IR (KBr): 1664, 1628, 1605, 1529, 1444, 1408, 1281,  
1252  $cm^{-1}$

35 NMR (DMSO- $d_6$ + $D_2O$ ,  $\delta$ ): 0.91 (3H, d,  $J=6.8Hz$ ), 0.98 (3H, d,  
 $J=6.8Hz$ ), 1.10 (3H, d,  $J=5.9Hz$ ), 1.3-2.7 (16H, m),  
2.8-4.5 (34H, m), 4.7-4.9 (2H, m), 6.7-6.9 (2H, m),  
6.9-7.1 (3H, m), 8.0-8.2 (4H, m), 8.73 (1H, d,  $J=2.6Hz$ )

ESI MASS (m/z) (Negative): 1408.5 (M-2H)<sup>2-</sup>

Elemental Analysis Calcd. for C<sub>63</sub>H<sub>87</sub>N<sub>13</sub>O<sub>20</sub>S<sub>2</sub>·8H<sub>2</sub>O:

C 48.67, H 6.68, N 11.71

Found: C 48.86, H 6.64, N 11.44

5

Example 66

IR (KBr): 1664, 1635, 1628, 1605, 1444, 1408, 1281,  
1259 cm<sup>-1</sup>

10 NMR (DMSO-d<sub>6</sub>+D<sub>2</sub>O, δ): 0.86 (3H, d, J=6.3Hz), 0.98 (3H, d,  
J=6.9Hz), 1.10 (3H, d, J=5.7Hz), 1.1-1.4 (5H, m),  
1.6-2.7 (11H, m), 2.8-4.5 (34H, m), 4.7-4.9 (2H, m),  
6.7-6.9 (2H, m), 6.9-7.1 (3H, m), 8.0-8.2 (4H, m), 8.72  
(1H, d, J=2.5Hz)

ESI MASS (m/z) (Negative): 1408.6 (M-2H)<sup>2-</sup>

15 Elemental Analysis Calcd. for C<sub>63</sub>H<sub>87</sub>N<sub>13</sub>O<sub>20</sub>S<sub>2</sub>·7H<sub>2</sub>O:

C 49.24, H 6.62, N 11.85

Found: C 49.05, H 6.73, N 11.48

Example 67

20 IR (KBr): 3352, 1664, 1635, 1603, 1444, 1408, 1281,  
1250 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>+D<sub>2</sub>O, δ): 0.85 (3H, t, J=7.4Hz), 0.98 (3H, d,  
J=6.8Hz), 1.10 (3H, d, J=5.9Hz), 1.3-2.6 (18H, m),  
2.8-4.5 (34H, m), 4.7-4.9 (2H, m), 6.7-6.9 (2H, m),  
25 6.9-7.1 (3H, m), 8.0-8.2 (4H, m), 8.73 (1H, d, J=2.6Hz)

ESI MASS (m/z) (Negative): 1423.5 (M<sup>-1</sup>)

Elemental Analysis Calcd. for C<sub>64</sub>H<sub>89</sub>N<sub>13</sub>O<sub>20</sub>S<sub>2</sub>·6H<sub>2</sub>O:

C 50.15, H 6.64, N 11.88

Found: C 49.99, H 6.74, N 11.61

30

Example 68

IR (KBr): 1664, 1628, 1603, 1529, 1444, 1408, 1281,  
1248 cm<sup>-1</sup>

35 NMR (DMSO-d<sub>6</sub>+D<sub>2</sub>O, δ): 0.7-1.3 (12H, m), 1.6-2.6 (15H, m),  
2.7-4.4 (34H, m), 4.7-4.9 (2H, m), 6.6-6.8 (2H, m),

6.8-7.0 (3H, m), 7.9-8.1 (4H, m), 8.66 (1H, d,  $J=2.5\text{Hz}$ )

ESI MASS (m/z) (Negative): 1423.5 ( $M^{-1}$ )

Elemental Analysis Calcd. for  $C_{64}H_{89}N_{13}O_{20}S_2 \cdot 6H_2O$ :

C 50.15, H 6.64, N 11.88

Found: C 49.95, H 6.74, N 11.47

5

#### Example 69

IR (KBr): 1658, 1635, 1549, 1529, 1518, 1468, 1446, 1277,  
1043  $\text{cm}^{-1}$

10

NMR (DMSO- $d_6$ + $D_2O$ ,  $\delta$ ): 0.97 (3H, d,  $J=6.8\text{Hz}$ ), 1.0-1.4 (9H, m), 1.5-2.6 (15H, m), 2.7-4.5 (31H, m), 4.7-4.9 (2H, m), 6.7-6.9 (2H, m), 7.0-7.1 (1H, m), 7.49 (2H, d,  $J=8.6\text{Hz}$ ), 7.8-8.1 (6H, m), 8.86 (1H, s)

ESI MASS (m/z) (Negative): 1432.4 ( $M^{-1}$ )

15

Elemental Analysis Calcd. for  $C_{66}H_{88}N_{12}O_{20}S_2 \cdot 6H_2O$ :

C 51.42, H 6.54, N 10.90

Found: C 51.36, H 6.65, N 10.50

#### Example 70

20

IR (KBr): 3493, 3462, 3433, 3350, 1659, 1635, 1613, 1529,  
1518, 1466, 1446  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ + $D_2O$ ,  $\delta$ ): 0.90 (3H, d,  $J=6.7\text{Hz}$ ), 0.98 (3H, d,  $J=6.6\text{Hz}$ ), 1.11 (3H, d,  $J=5.3\text{Hz}$ ), 1.3-2.7 (16H, m), 2.8-4.5 (34H, m), 4.7-4.9 (2H, m), 6.7-6.9 (2H, m), 7.0-7.2 (3H, m), 7.78 (2H, d,  $J=8.7\text{Hz}$ ), 7.9-8.1 (4H, m), 8.78 (1H, s)

25

ESI MASS (m/z) (Negative): 1447.5 ( $M^{-1}$ )

Elemental Analysis Calcd. for  $C_{66}H_{89}N_{13}O_{20}S_2 \cdot 8H_2O$ :

C 49.77, H 6.64, N 11.43

Found: C 50.09, H 6.68, N 11.14

30

#### Example 71

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.8-2.8 (40H, m), 2.8-4.6 (28H, m), 4.7-5.4 (9H, m), 6.6-6.85 (2H, m), 6.9-7.1 (3H, m), 7.3-8.5 (12H, m), 8.6-8.8 (2H, m)

35

MASS (m/z): 1391 ( $M^+-1$ )

Elemental Analysis Calcd. for  $C_{67}H_{96}N_{10}O_{20}S \cdot 7H_2O$ :

C 52.95, H 7.30, N 9.22

Found: C 52.88, H 7.33, N 9.22

5

The following compound was obtained according to a similar manner to that of Example 54.

Example 72

10 NMR (DMSO- $d_6$ +D<sub>2</sub>O,  $\delta$ ): 0.7-4.5 (67H, m), 4.65-4.85 (2H, m),  
6.3-6.45 (1H, m), 6.5-6.7 (2H, m), 7.12 (2H, d,  
J=8.8Hz), 7.6-7.8 (4H, m), 7.95 (2H, d, J=8.4Hz)

ESI MASS (m/z): 1311 ( $M^+-1$ )

Elemental Analysis Calcd. for  $C_{67}H_{96}N_{10}O_{17} \cdot 3HCl \cdot 10H_2O$ :

15 C 50.20, H 7.48, N 8.74

Found: C 50.28, H 7.15, N 8.67

The following compounds [Examples 73 to 87] were obtained according to a similar manner to that of Example 33.

20

Example 73

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.84 (9H, s), 0.97 (3H, d, J=7.0Hz),  
1.0-1.4 (8H, m), 1.6-2.8 (18H, m), 2.8-4.6 (28H, m),  
4.7-5.4 (9H, m), 6.6-6.8 (2H, m), 6.9-7.1 (3H, m),  
25 7.3-8.5 (12H, m), 8.6-8.8 (2H, m)

MASS (m/z): 1365 ( $M^+-1$ )

Elemental Analysis Calcd. for  $C_{65}H_{94}N_{10}O_{20}S \cdot 7H_2O$ :

C 52.27, H 7.29, N 9.38

Found: C 52.15, H 7.30, N 9.30

30

Example 74

IR (KBr): 1649, 1539, 1514, 1454, 1439, 1045  $cm^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.7-1.4 (16H, m), 1.6-2.8 (18H, m),  
2.8-4.6 (28H, m), 4.7-5.5 (9H, m), 6.6-6.8 (2H, m),  
35 6.9-7.1 (3H, m), 7.3-8.5 (12H, m), 8.5-8.8 (2H, m)

MASS (m/z): 1337 ( $M^{+1}$ )

Elemental Analysis Calcd. for  $C_{63}H_{90}N_{10}O_{20}S_9H_2O$ :

C 50.39, H 7.25, N 9.33

Found: C 50.64, H 6.96, N 9.24

5

Example 75

IR (KBr): 1666, 1649, 1632, 1539, 1514, 1454, 1238  $cm^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.85 (3H, t,  $J=7.0Hz$ ), 0.97 (3H, d,  $J=6.6Hz$ ), 1.09 (3H, d,  $J=5.5Hz$ ), 1.2-2.75 (25H, m), 2.8-4.6 (28H, m), 4.7-5.4 (9H, m), 6.6-6.8 (2H, m), 6.9-7.1 (3H, m), 7.3-8.5 (12H, m), 8.6-8.8 (2H, m)

10

MASS (m/z): 1337 ( $M^{+1}$ )

Elemental Analysis Calcd. for  $C_{63}H_{90}N_{10}O_{20}S_9H_2O$ :

C 51.63, H 7.15, N 9.56

Found: C 51.74, H 7.07, N 9.52

15

Example 76

IR (KBr): 1666, 1649, 1632, 1539, 1514, 1236  $cm^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.98 (3H, d,  $J=6.6Hz$ ), 1.10 (3H, d,  $J=5.7Hz$ ), 2.8-4.6 (64H, m), 4.7-5.4 (9H, m), 6.6-6.85 (2H, m), 6.9-7.15 (3H, m), 7.3-8.5 (12H, m), 8.6-8.8 (2H, m)

20

MASS (m/z): 1421 ( $M^{+1}$ )

Elemental Analysis Calcd. for  $C_{68}H_{98}N_{10}O_{21}S_8H_2O$ :

C 52.10, H 7.33, N 8.93

Found: C 52.18, H 7.22, N 8.85

25

Example 77

30 Example 78

IR (KBr): 1666, 1632, 1539, 1514, 1452, 1236  $cm^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.7-2.7 (38H, m), 2.8-4.6 (32H, m), 4.7-5.4 (9H, m), 6.6-6.85 (3H, m), 6.9-7.1 (2H, m), 7.3-8.5 (12H, m), 8.6-8.8 (2H, m)

35

MASS (m/z): 1421 ( $M^{+1}$ )

Elemental Analysis Calcd. for  $C_{68}H_{98}N_{10}O_{21}S \cdot 8H_2O$ :

C 52.10, H 7.33, N 8.94

Found: C 52.10, H 7.17, N 9.33

5 Example 79

IR (KBr): 1632, 1539, 1516, 1452, 1238  $cm^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.8-1.4 (16H, m), 1.6-2.8 (22H, m),  
2.8-5.55 (32H, m), 4.7-5.4 (9H, m), 6.65-6.85 (2H, m),  
6.9-7.1 (3H, m), 7.3-8.5 (12H, m), 8.5-8.8 (2H, m)

10 MASS (m/z): 1421 ( $M^+-1$ )

Elemental Analysis Calcd. for  $C_{68}H_{98}N_{10}O_{21}S \cdot 8H_2O$ :

C 52.10, H 7.33, N 8.94

Found: C 51.82, H 7.17, N 9.23

15 Example 80

IR (KBr): 1666, 1645, 1632, 1539, 1514, 1452, 1240  $cm^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.98 (3H, d,  $J=6.8Hz$ ), 1.10 (3H, d,  
 $J=5.5Hz$ ), 1.4-2.75 (23H, m), 2.8-4.5 (31H, m), 4.7-5.4  
(9H, m), 6.65-6.9 (4H, m), 6.9-7.1 (3H, m), 7.15 (2H,  
20 d,  $J=8.7Hz$ ), 7.3-8.5 (12H, m), 8.6-8.8 (2H, m)

MASS (m/z): 1415 ( $M^+-1$ )

Elemental Analysis Calcd. for  $C_{68}H_{92}N_{10}O_{21}S \cdot 12H_2O$ :

C 49.99, H 7.16, N 8.57

Found: C 49.86, H 6.81, N 8.96

25

Example 81

IR (KBr): 1632, 1539, 1514, 1452, 1275  $cm^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 0.97 (3H, d,  $J=6.7Hz$ ), 1.10 (3H, d,  
 $J=5.7Hz$ ), 1.2-2.8 (23H, m), 2.8-4.55 (31H, m), 4.7-5.4  
30 (9H, m), 6.6-6.9 (4H, m), 6.9-7.1 (3H, m), 7.14 (2H,  
d,  $J=8.7Hz$ ), 7.3-8.5 (12H, m) 8.6-8.8 (2H, m)

MASS (m/z): 1415 ( $M^+-1$ )

Elemental Analysis Calcd. for  $C_{68}H_{92}N_{10}O_{21}S \cdot 8H_2O$ :

C 52.30, H 6.97, N 8.97

Found: C 52.48, H 6.79, N 9.44

35

Example 82

IR (KBr): 1676, 1649, 1632, 1539, 1514, 1456, 1236  $\text{cm}^{-1}$   
NMR (DMSO- $\text{d}_6$ ,  $\delta$ ): 0.88 (6H, s), 0.97 (3H, d,  $J=6.6\text{Hz}$ ), 1.10  
5 (3H, d,  $J=5.4\text{Hz}$ ), 1.1-2.8 (22H, m), 2.8-4.6 (28H, m),  
4.7-5.5 (9H, m), 6.6-6.8 (2H, m), 6.9-7.1 (3H, m),  
7.3-8.8 (14H, m)  
MASS (m/z): 1339 ( $\text{M}^+ + 1$ )  
Elemental Analysis Calcd. for  $\text{C}_{63}\text{H}_{90}\text{N}_{10}\text{O}_{20}\text{S}_8\text{H}_2\text{O}$ :  
10 C 51.00, H 7.20, N 9.44  
Found: C 51.31, H 7.16, N 9.44

Example 83

IR (KBr): 1664, 1635, 1626, 1605, 1446, 1408, 1350,  
15 1329  $\text{cm}^{-1}$   
NMR (DMSO- $\text{d}_6 + \text{D}_2\text{O}$ ,  $\delta$ ): 0.98 (3H, d,  $J=6.8\text{Hz}$ ), 1.09 (3H, d,  
 $J=5.7\text{Hz}$ ), 1.2-2.8 (24H, m), 2.8-4.5 (37H, m), 4.7-  
4.9 (2H, m), 6.7-6.9 (2H, m), 7.0-7.1 (3H, m), 7.62  
(2H, d,  $J=8.7\text{Hz}$ ), 7.70 (2H, d,  $J=8.4\text{Hz}$ ), 7.93 (2H, d,  
20  $J=8.4\text{Hz}$ )  
ESI MASS (m/z) (Negative): 1407.6 ( $\text{M}-2\text{H}$ ) $^{2-}$   
Elemental Analysis Calcd. for  $\text{C}_{67}\text{H}_{96}\text{N}_{10}\text{O}_{21}\text{S}_6\text{H}_2\text{O}$ :  
C 53.02, H 7.17, N 9.23  
Found: C 52.98, H 7.28, N 9.13

Example 84

IR (KBr): 1664, 1628, 1606, 1531, 1497, 1446, 1281, 1238  
 $\text{cm}^{-1}$   
NMR (DMSO- $\text{d}_6 + \text{D}_2\text{O}$ ,  $\delta$ ): 0.97 (3H, d,  $J=6.7\text{Hz}$ ), 1.10 (3H, d,  
30  $J=5.4\text{Hz}$ ), 1.3-2.7 (24H, m), 2.8-4.5 (37H, m), 4.7-  
4.9 (2H, m), 6.7-6.9 (2H, m), 7.0-7.2 (3H, m), 7.62  
(2H, d,  $J=8.6\text{Hz}$ ), 7.70 (2H, d,  $J=8.5\text{Hz}$ ), 7.93 (2H, d,  
 $J=8.5\text{Hz}$ )  
ESI MASS (m/z) (Negative): 1408.4 ( $\text{M}^- - 1$ )  
35 Elemental Analysis Calcd. for  $\text{C}_{67}\text{H}_{96}\text{N}_{10}\text{O}_{21}\text{S}_5\text{H}_2\text{O}$ :



C 53.66, H 7.12, N 9.34

Found: C 53.58, H 7.34, N 9.15

Example 85

- 5 IR (KBr): 1664, 1628, 1606, 1529, 1497, 1446, 1408, 1281,  
1238  $\text{cm}^{-1}$
- NMR ( $\text{DMSO}-d_6 + \text{D}_2\text{O}$ ,  $\delta$ ): 0.97 (3H, d,  $J=6.9\text{Hz}$ ), 1.10 (3H, d,  
 $J=6.0\text{Hz}$ ), 1.5-4.5 (52H, m), 4.7-4.9 (2H, m), 6.7-6.9  
10 (2H, m), 6.9-7.1 (3H, m), 7.2-7.5 (5H, m), 7.62 (2H,  
d,  $J=8.6\text{Hz}$ ), 7.71 (2H, d,  $J=8.6\text{Hz}$ ), 7.93 (2H, d,  
 $J=8.3\text{Hz}$ )
- ESI MASS ( $m/z$ ) (Negative): 1415.4 ( $M-2H$ )<sup>2-</sup>  
Elemental Analysis Calcd. for  $\text{C}_{68}\text{H}_{92}\text{N}_{10}\text{O}_{21}\text{S}_6\text{H}_2\text{O}$ :  
C 53.53, H 6.87, N 9.18  
15 Found: C 53.55, H 6.91, N 9.00

Example 86

- NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 0.9 (3H, d,  $J=6.8\text{Hz}$ ), 0.98 (3H, d,  $J=6.8\text{Hz}$ ),  
1.10 (3H, d,  $J=6.1\text{Hz}$ ), 1.3-2.7 (24H, m), 2.8-4.6 (29H,  
20 m), 4.7-5.3 (9H, m), 6.6-6.8 (2H, m), 6.9-7.2 (3H, m),  
7.3-8.2 (11H, m), 8.4-8.6 (1H, m), 8.7 (1H, s),  
8.8-8.95 (1H, m)
- MASS ( $m/z$ ): 1421 ( $M^+-1$ )  
Elemental Analysis Calcd. for  $\text{C}_{65}\text{H}_{90}\text{N}_{12}\text{O}_{20}\text{S}_2\text{H}_2\text{O}$ :  
C 49.80, H 6.81, N 10.72  
25 Found: C 50.07, H 6.74, N 10.73

Example 87

- IR (KBr): 3351.7, 2931.3, 2854.1, 1658.5, 1635.3, 1546.6,  
30 1531.2, 1496.5  $\text{cm}^{-1}$
- NMR ( $\text{DMSO}-d_6 + \text{D}_2\text{O}$ ,  $\delta$ ): 0.97 (3H, d,  $J=7\text{Hz}$ ), 0.8-4.5 (65H,  
complex m), 3.01 (3H, s), 4.79-4.81 (2H, m), 6.72 (1H,  
d,  $J=8\text{Hz}$ ), 6.75-6.80 (1H, m), 7.01 (1H, s), 7.03 (2H,  
d,  $J=8\text{Hz}$ ), 7.61 (2H, d,  $J=8\text{Hz}$ ), 7.69 (2H, d,  $J=8.4\text{Hz}$ ),  
35 7.94 (2H, d,  $J=8.4\text{Hz}$ )

ESI MASS (m/z) (Negative): 1435.7 ( $M^{+}-1$ )

Example 88

To a solution of a mixture of starting compound (88) (7.5 g), 1,3-dihydroxyacetone (1.19 g) and acetic acid (1.14 ml) in a mixture of methanol (120 ml) and DMF (55 ml) was added sodium cyanoborohydride (835 mg) with stirring at ambient temperature, and the mixture was stirred at the same temperature overnight. To a reaction mixture was poured into ethyl acetate (700 ml). The resulting precipitates were collected by filtration, washed with ethyl acetate (100 ml) and dried in vacuo. The precipitates were dissolved in a mixture of 30% aqueous acetonitrile (800 ml) and 1N sodium hydroxide (5 ml). The solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (440 ml) eluting in turn with water and aqueous acetonitrile (30%-60%). The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (88) (5.22 g).

IR (KBr): 1632, 1535, 1518, 1443, 1269, 1082, 1047  $\text{cm}^{-1}$

NMR ( $\text{DMSO}-d_6 + \text{D}_2\text{O}$ ,  $\delta$ ): 0.82 (3H, d,  $J=6.83\text{Hz}$ ), 0.97 (3H, d,  $J=6.81\text{Hz}$ ), 1.02 (3H, d,  $J=6.18\text{Hz}$ ), 1.24 (26H, s), 1.35-2.45 (14H, m), 2.75-3.40 (5H, m), 3.60-4.50 (15H, m), 4.70-4.90 (2H, m), 6.65-6.80 (2H, m), 7.01 (1H, s)

ESI MASS (m/z) (Positive): 1088.4 ( $M^{+} + \text{Na}$ )

Example 89

To a solution of starting compound (89) (4.0 g) in DMF (40 ml) were successively added diisopropylethylamine (1.45 ml) and 9-fluorenylmethyl chloroformate (1.03 g), and the mixture was stirred at ambient temperature for 2 hours. The reaction mixture was poured into water (200 ml). The solution was purified by ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (200 ml) column chromatography, eluting in turn

with a mixture of saturated aqueous sodium chloride (400 ml), saturated aqueous sodium hydrogen carbonate (50 ml) and water (400 ml), and aqueous acetonitrile (30-60%). The fractions containing the object compound were collected and evaporated  
5 under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (89) (2.82 g).

IR (KBr): 1666, 1632, 1518, 1446, 1273, 1246, 1082,  
1047  $\text{cm}^{-1}$

10 NMR ( $\text{DMSO}-d_6 + \text{D}_2\text{O}$ ,  $\delta$ ): 0.80-1.10 (9H, m), 1.23 (26H, s), 1.35-2.45 (12H, m), 2.60-3.40 (6H, m), 3.60-4.55 (18H, m), 4.65-4.90 (2H, m), 6.65-6.85 (2H, m), 6.97 (1H, s), 7.30-7.50 (4H, m), 7.60-7.95 (4H, m)

ESI MASS ( $m/z$ ) (Negative): 1423.7 ( $\text{M}^+ - \text{Na}$ )

Elemental Analysis Calcd. for  $\text{C}_{69}\text{H}_{99}\text{N}_6\text{O}_{22}\text{SNa} \cdot 6\text{H}_2\text{O}$ :

15 C 53.27, H 7.19, N 7.20  
Found: C 53.45, H 7.21, N 7.10

#### Example 90

To a solution of starting compound (90) (1.21 g) in DMF (15  
20 ml) were successively added diisopropylethylamine (0.26 ml) and di-tert-butyl dicarbonate (285 mg) and the mixture was stirred at ambient temperature overnight. The reaction mixture was poured into a mixture of pH 6.86 standard buffer solution (150  
25 ml), saturated aqueous sodium chloride (50 ml) and saturated aqueous sodium hydrogen carbonate (20 ml). The mixture was purified by ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (200 ml) column chromatography, eluting with aqueous acetonitrile (30-50%). The fractions  
30 containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (90) (1.19 g).

IR (KBr): 1662, 1632, 1535, 1518, 1444, 1367, 1272,  
1250  $\text{cm}^{-1}$

35 NMR ( $\text{DMSO}-d_6 + \text{D}_2\text{O}$ ,  $\delta$ ): 0.85 (3H, d,  $J=6.76\text{Hz}$ ), 0.96 (3H, d,  $J=6.77\text{Hz}$ ), 1.04 (3H, d,  $J=5.50\text{Hz}$ ), 1.23 (26H, s), 1.37

(9H, s), 1.40-1.50 (2H, m), 1.55-2.50 (10H, m),  
2.80-3.40 (6H, m), 3.50-4.45 (14H, m), 6.65-6.80 (2H,  
m), 6.96 (1H, s)

ESI MASS (m/z) (Negative): 1301.6 ( $M^+$ -Na)

5

#### Example 91

To a solution of a mixture of starting compound (91) (2.0 g), 2-phenyl-1,3-dioxane-5-carbaldehyde (0.52 g) and acetic acid (0.35 ml) in a mixture of methanol (30 ml) and DMF (14 ml) was added sodium cyanoborohydride (254 mg) with stirring at ambient temperature and the mixture was stirred at the same temperature for 6 hours. The reaction mixture was poured into ethyl acetate (300 ml). The resulting precipitates were collected by filtration, washed with ethyl acetate (50 ml) and dried in vacuo. The precipitates were dissolved with pH 6.86 standard buffer solution (100 ml) and acetonitrile (200 ml) and the solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (220 ml) eluting in turn with water (1 L), 20% acetonitrile in water and 30% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (91) (2.27 g).

NMR (DMSO- $d_6$ +D<sub>2</sub>O,  $\delta$ ): 0.96 (3H, d, J=6.56Hz), 1.07 (3H, d, J=5.42Hz), 1.33, 1.37 (9H, broad s), 1.50-2.05 (6H, m), 2.10-2.45 (2H, m), 2.60-3.50 (6H, m), 3.75-4.50 (16H, m), 4.75-4.85 (2H, m), 5.44, 5.55 (1H, broad s), 6.75 (2H, m), 7.38 (5H, br s)

ESI MASS (m/z) (Negative): 1189.3 ( $M^+$ +Na)

30

#### Example 92

A solution of starting compound (92) (2.26 g), 10% palladium on carbon (50% including water) (2.0 g) and 10% palladium hydroxide on carbon (2.0 g) in a mixture of methanol (45 ml) and water (23 ml) was hydrogenated under an atmospheric pressure of

35

hydrogen with stirring at ambient temperature for 6 hours. The catalyst was filtered off and washed with a mixture of methanol and water (1:1 v/v) (50 ml), and the filtrates were combined. The mixture was evaporated in vacuo and dissolved in water (200 ml). The solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (220 ml) eluting with water and 30% acetonitrile in water. The first fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (92) (1.84 g).

NMR (DMSO- $d_6$ +D<sub>2</sub>O,  $\delta$ ): 0.97 (3H, d, J=6.75Hz), 1.07 (3H, d, J=5.76Hz), 1.35 (9H, s), 1.45-2.00 (6H, m), 2.10-2.45 (3H, m), 2.70-3.45 (9H, m), 3.55-4.55 (17H, m), 4.75-4.85 (2H, m), 6.65-6.80 (2H, m), 7.02 (1H, s)  
ESI MASS (m/z) (Positive): 1123.3 (M<sup>+</sup>+Na), 1101.3 (M<sup>+</sup>+2Na),

### Example 93

To a solution of a mixture of starting compound (93) (1.83 g) and diisopropylethylamine (0.65 ml) in DMF (20 ml) was added 9-fluorenylmethyloxycarbonyl chloride (483 mg) with stirring at ambient temperature and the mixture was stirred at the same temperature for 2 hours. The reaction mixture was poured into water (300 ml). The mixture was adjusted to pH 7.5 with 1N HCl and washed with ethyl acetate (100 ml). The aqueous layer was evaporated to remove organic solvent. To a concentrated solution were added saturated aqueous sodium hydrogen carbonate (50 ml) and 5% aqueous sodium chloride (20 ml). The solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (220 ml) eluting in turn with water (1 L), 20% acetonitrile in water (1 L) and 30% acetonitrile in water (1 L). The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (93) (2.106 g)

NMR (DMSO- $d_6$ +D<sub>2</sub>O,  $\delta$ ): 0.89 (3H, br s), 1.07 (3H, br s), 1.34 (9H, s), 1.45-2.50 (10H, m), 2.60-3.40 (13H, m), 3.70-4.50 (14H, m), 4.65-4.90 (2H, m), 6.65-6.80 (2H, m), 6.99 (1H, s), 6.95-7.48 (4H, m), 7.60-7.70 (2H, m), 7.85-7.95 (2H, m)

ESI MASS (m/z) (Positive): 1345.3 ( $M^+$ +Na)

#### Example 94

To a solution of a mixture of starting compound (94) (2.10 g) and triethylsilane (2.03 ml) in dichloromethane (35 ml) was dropwise added trifluoroacetic acid (3.70 ml) with stirring under ice-cooling and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was poured into a mixture of pH 6.86 standard buffer solution (150 ml) and saturated aqueous sodium hydrogen carbonate (20 ml). The mixture was adjusted to pH 8 with saturated aqueous sodium carbonate. The organic layer was separated and concentrated in vacuo to remove organic solvent. The solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (220 ml) eluting in turn with water (1 L), 10% acetonitrile in water (800 ml), 20% acetonitrile in water (1 L) and then 30% acetonitrile in water (1 L). The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (94) (1.704 g).

IR (KBr): 1668, 1633, 1539, 1516, 1440, 1273, 1082, 1045  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ +D<sub>2</sub>O,  $\delta$ ): 0.89 (3H, br s), 1.05-1.20 (3H, m), 1.30-2.40 (8H, m), 2.60-3.40 (10H, m), 3.50-4.45 (16H, m), 4.60-4.85 (2H, m), 6.73 (2H, br s), 6.97 (1H, s), 7.25-7.48 (4H, m), 7.66 (2H, d,  $J=7.12\text{Hz}$ ), 7.88 (2H, d,  $J=7.24\text{Hz}$ )

ESI MASS (m/z) (Positive): 1199.4 ( $M^+$ +1), 1200.4 ( $M^+$ )

Elemental Analysis Calcd. for  $\text{C}_{54}\text{H}_{84}\text{N}_8\text{O}_{27}\text{S}\cdot 6\text{H}_2\text{O}$ :

C 49.53, H 6.47, N 8.56

Found: C 49.30, H 6.26, N 8.49

The following compound was obtained according to a similar  
5 manner to that of Example 33.

Example 95

IR (KBr): 1664, 1628, 1605, 1446, 1417, 1279, 1084,  
1047  $\text{cm}^{-1}$

10 NMR (DMSO- $d_6$ +D<sub>2</sub>O,  $\delta$ ): 0.8-1.3 (12H, m), 1.5-2.6 (16H, m),  
2.8-4.5 (32H, m), 4.7-4.9 (2H, m), 6.7-6.9 (2H, m),  
7.0-7.2 (3H, m), 7.85 (2H, d,  $J=8.6\text{Hz}$ ), 8.0-8.2 (4H,  
m)

ESI MASS (m/z) (Negative): 1423.5 ( $M^{-1}$ )

15

20

25

30